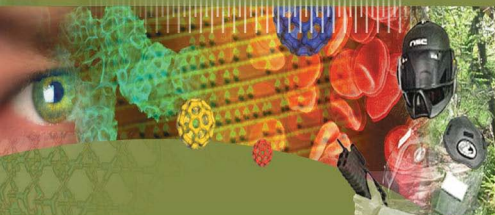


Margaret E. Kosal

Nanotechnology for Chemical and Biological Defense



Nanotechnology for Chemical and Biological Defense

Margaret E. Kosal

Nanotechnology for Chemical and Biological Defense

 Springer

Margaret E. Kosal
Georgia Institute of Technology
Sam Nunn School of International Affairs
Center for International Strategy, Technology, and Policy
Atlanta, GA 30332
USA
margaret.kosal@inta.gatech.edu

ISBN 978-1-4419-0061-6 e-ISBN 978-1-4419-0062-3
DOI 10.1007/978-1-4419-0062-3
Springer Dordrecht Heidelberg London New York

Library of Congress Control Number: 2009926040

© Springer Science+Business Media, LLC 2009

All rights reserved. This work may not be translated or copied in whole or in part without the written permission of the publisher (Springer Science+Business Media, LLC, 233 Spring Street, New York, NY 10013, USA), except for brief excerpts in connection with reviews or scholarly analysis. Use in connection with any form of information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed is forbidden.

The use in this publication of trade names, trademarks, service marks, and similar terms, even if they are not identified as such, is not to be taken as an expression of opinion as to whether or not they are subject to proprietary rights.

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

New and unpredicted technologies are emerging at an unprecedented pace around the world. Communication of those new discoveries is occurring faster than ever, meaning that the unique ownership of a piece of new technology is no longer a sufficient position, if not impossible. In today's world, recognition of the potential applications of a technology and a sense of purpose in exploiting it are far more important than simply having access to it.

Technological surprise has and will continue to take many forms. A plethora of new technologies are under development for peaceful means but may have unintended security consequences and will certainly require innovative countermeasures. A relevant example is the tremendous development in biotechnology that has occurred since the advent of recombinant DNA and tissue culture-based processes in the 1970s. If US government agencies and the defense and academic communities had more clearly recognized the potential for biotechnology to affect fundamental security and warfighting doctrines 20 years ago, the situation today could be very different. Defense against chemical and biological weapons – from both states and nonstate actors – currently presents a threat that is difficult to predict and for which traditional solutions are increasingly less effective.

Nanotechnology has emerged as a well-funded discipline that, like biotechnology, carries the potential for groundbreaking applications and the potential for unpredictable harm. The world is likely 20 years away from the full impact of the nanotechnology on defensive capabilities. Now is therefore the time to explore the potential for new science and new breakthroughs, and now is the time to begin the strategic thinking needed to achieve, exploit, and defend against these discoveries.

The ability to preempt technological surprise by forward thinking is a tempting goal. Making accurate predictions, however, is never easy and can many times be dangerous. For these reasons, any attempt to look forward more than 20 years must be driven by strategic concerns as well as deep knowledge, flexible thinking, and sound tactics.

Scope and Purpose

The research underpinning this book, and the workshop that was undertaken as part of it, was intended to better enable an informed national debate and to affect international debate on the potential role and impact of nanotechnology and emerging science on national defense and homeland and international security. The text highlights the findings and conclusions from the study and accompanying workshop as well as identifies research directions in basic and applied science that may foster transformational breakthroughs in nanotechnology-based chemical and biological countermeasures. This ambitious effort serves manifold objectives, including the following:

- To give policymakers a strategic roadmap to provide a basis for research direction decisions for chemical and biological nanotechnology countermeasures
- To provide an overview of the current and future challenges associated with chemical and biological defense, both for military operations and for homeland security applications
- To provide a survey of potential future proliferation and malevolent cooption of emerging technologies, such as nanotechnology, incorporating a robust technical perspective
- To consider the impact of the changing threat environment in which the military operates and the implications for fostering innovative research support for chemical and biological countermeasures
- To highlight current successes and challenges in the organizational structure and management of chemical and biological defense-related research as well as nanotechnology-related research at the federal level

This study and workshop emphasized revolutionary rather than evolutionary science and technology. Evolutionary developments refer to foreseeable and incremental improvements in a technological capability based on the current state of the art. Revolutionary or breakthrough science is that which changes the current way of thinking about solving a problem, specifically chemical and biological defense in this application. Some historical examples of revolutionary technologies are the understanding the role and structure of DNA, the use of genetic engineering, and the capability of electron microscopy to “see” with electrons rather than light.

Further, the study and workshop intentionally spanned both technical disciplines and the social sciences. Ideas or work from across the experimental and theoretical physical and life sciences are included and contributions of social scientists were actively sought. To paraphrase Secretary of Defense Robert Gates,¹ the challenges facing the world require a much broader conception than during the Cold War, and the solutions will require application and engagement of additional intellectual disciplines that transverse previous conceptions of interdisciplinary.

Chapters 1 and 2 provide an overview of the current situation and provide detailed background on the “four worlds” construct – the scenarios – used to frame the study. Chapter 3 describes the potential applications for nanotechnology in specific areas of CB defense – physical protection, detection and diagnostics, decontamination, and medical countermeasures. Chapter 4 examines the potential for intentional misuse of nanotechnology in the chem-bio regime. Chapter 5 outlines near-term research directions, and Chapter 6 provides a summary and concluding remarks.

Chapters 3–5 delve into a level of detail directed toward the scientific community. Technical references to specific documents and leading scholarly journals are included for the reader who is interested in more closely examining the ideas upon which the text, scenarios, conclusions, and recommendations are based.

Acknowledgments

This effort was initiated while the author served as Science and Technology Advisor in the Office of the Secretary of Defense as an American Association for the Advancement of Science (AAAS) Fellow.

The following persons are gratefully acknowledged for making this effort a success:

- Kenneth Cole, Devon Byrd, Amanda Dion-Schultz, Ben Hagar, Rick Jaffe, Christophe McCray, Jeff Owens, Christian Whitchurch, and Lloyd Whitman, who served as focus group leaders at the workshop and provided expert commentary and review on the resulting text
- Arnie Baker, Esther Chang, Vicki Colvin, John Doesburg, David Gorenstein, James Heath, Craig Hill, Peter Hobart, A.T. Charlie Johnson, J. Rogers Hollingsworth, Martin Moskovits, Cengiz Ozkan, Mike Penny, Jean Reed, Michael Strano, Z.L. Wang, and Omar Yaghi, who made presentations at the workshop and offered other advice or comments
- George Bachand, Pat Black, James Harmon, Mike Kaminski, Ken Klabunde, Don Leo, Jennifer Martinez, James Murday, Aleksandr Noy, Renee Gonzales Sells, Sharon Shields, and Jeff Tsao, who served as rapporteurs and contributors to the project
- Toni Marechaux, Amy Hoang-Wrona, and Sarah Canna for invaluable editorial and organizational assistance

While this project has been sponsored by the Defense Threat Reduction Agency's Chemical and Biological Technologies Directorate (DTRA-CB) and the Office of the Special Assistant for Chemical and Biological Defense and Chemical Demilitarization Programs (OSA(CBD&CDP)) within the Office of the Secretary of Defense (OSD), it does not represent official US Government, Department of Defense, Defense Threat Reduction Agency, or Chemical and Biological Defense Program policy or opinion. All errors and opinion are the responsibility of the author. Finally, the author would like to acknowledge specifically Fred Crowson and Jerry Pate, from DTRA-CB physical science and technology division, for generous and continued support.

Note

1. Speech as delivered by Secretary of Defense Robert M. Gates to the Association of American Universities (Washington, DC), April 14, 2008, <http://www.defenselink.mil/speeches/speech.aspx?speechid=1228>. Accessed 30 June 2008.

Contents

Introduction	xiii
1 Framing the Opportunities and the Challenges	1
Responding to a New Threat Environment	1
The Changing Nature of Warfare	2
The Changing Nature of Technological Progress	4
Globalization as a Driver	4
Revolutionary Technology on the Nanoscale	5
From Science to Application	6
International Investments in Nanotechnology	7
Unintended Consequences	8
Other Critical Factors	9
Underlying Needs of the Operator	9
Relationship Between Science and National Security	10
Evolving Federal Guidance	12
Executive Agency Directives	13
Notes and References	15
2 Implementing the Process	19
Scenario-Based Planning	20
The Process	21
Creation of 2030 Worlds	23
Envisioning Scenarios in the Four Worlds	24
Using Scenarios to Roadmap and Prioritize	26
Value of This Approach	26
References	27
3 Applying Nanotechnology to Revolutionary	
Chemical and Biological Countermeasures	29
Progress at the Nanoscale	29
Physical Protection	30

Implications of Advances via Nanotechnology	32
Possible Solutions in 2030	33
Pathways to Achieve Physical Protection	38
Detection and Diagnostics of Chemical and Biological Agents.....	43
Methods.....	43
Potential Improvements in 2030	52
Pathways to Achieve CB Countermeasures	57
Decontamination	63
Postexposure Protection and Decontamination	64
Pre-exposure Protection and Decontamination.....	70
Wide-Area Decontamination and Demilitarization	70
A Path Forward	71
Medical Countermeasures.....	71
Countermeasures.....	73
Technical Challenges	78
From Capability Needs to Research Priorities.....	80
Notes and References.....	81
4 Potential Malfeasant Cooption of Nanotechnology.....	89
Novel Nanotechnology-Enabled Biochemical Weapons	90
Nanoparticles with Toxic or Deleterious Health Effects.....	93
Bio- and Nanoenabled Influence Operations	95
Nanotechnology-Enabled Evasion of Medical Countermeasures.....	96
Self-Assembled Materials and Devices and	
Potential Molecular Assemblers	97
Notes and References.....	99
5 Strategic Research Priorities and Directions.....	103
Structure and Function of Nanomaterials	105
Understanding and Controlling Nanoscale	
Properties and Reactivity	105
Understanding Properties and Reactivity	
Related to Physiology	107
Systems Biology	108
The Interface with Biological Systems: “Bridging the	
Bio- and Nano Worlds”	110
Self-Assembly, In Vivo and In Vitro.....	112
Modeling and Simulation.....	113
Power and Energy	114
Systems Integration and Engineering	115
Translational Medicine	117
Notes and References.....	118

6 The Need to Foster Revolutionary Science	121
Evolving Threats and Driving Forces	121
The Need for Strategic Vision.....	122
Fostering Breakthrough Discoveries.....	123
Challenges in Coordination of CB Defense Research	125
Inter- and Intra-Agency Coordination of Nanotechnology	126
Technology Planning	127
International Coordination	128
Looking Forward.....	128
Notes and References.....	130

Appendices

A Roles and Missions of Chemical and Biological Defense Organizations	135
B Attendees at the Workshop on Nanotechnology for Chemical and Biological Defense	141
C Agenda for the Workshop on Nanotechnology for Chemical and Biological Defense	147
D Acronyms and Abbreviations	151

Index.....	155
-------------------	------------

Introduction

I have always been interested in technology and its linkage to strategic thought and direction. As the Commanding General for the US Army Soldier and Biological Chemical Defense Command and later the US Army Research, Development and Engineering Command, I was concerned that potential disruptive technologies were not being given in-depth thought and analysis. For one beautiful winter week in Santa Fe, NM, I had the opportunity to be involved in a workshop which brought together research scientists, military laboratory technologists, warfighters, intelligence analysts, and social scientists to look at the future role nanotechnology might play in chemical and biological defense, and more importantly, its potential perils for national security.

The results of that study (along with many hours of the author) are captured in *Nanotechnology for Chemical and Biological Defense*. This seminal document is the first technically robust consideration of potential proliferation threats of nanotechnology for chemical and biological weapons, both by states and terrorists and the first prioritization of the threats from a technical and operational perspective. It clearly addresses all issues of chemical and biological defense from detection, decontamination, protection, and medical defense and provides a visionary roadmap for strategic investment in nanotechnology and emerging sciences to enable revolutionary countermeasures for chemical and biological defense. More importantly, it provides a concise picture which enables anticipation of potential proliferation challenges.

As you read the text, you will note several shifts in thought from traditional military operations to stability operations; the role of technology in asymmetric warfare against nontraditional adversaries; and homeland defense and homeland security. These shifts help define what may be the changing context of chemical and biological defense as we currently know it. Additionally, it helps to predict a strategic context for the “war after next, after next, after next...” without limiting us to a vision that is only predicated on a slight change from the world of today – truly a look at revolutionary change not evolutionary change.

Finally, *Nanotechnology for Chemical and Biological Defense* also addresses the programmatic issues and human factors that underpin scientific breakthroughs with a critical review of how we, as a nation, might want to go forward. Specific attention is paid to national level coordination on chemical, biological

and nanotechnology research and development planning and funding and the importance of understanding what is on the leading edge of basic research in all three areas.

I encourage you to spend some time reading, in detail, this document. It is clearly the best treatise on a disruptive technology and its potential impact, particularly with regard to chemical and biological defense.

John Doesburg
Major General US Army (ret)
and Principal Associate Director for Global Security
Lawrence Livermore National Laboratory (LLNL)

Chapter 1

Framing the Opportunities and the Challenges

From the chlorine gas attacks of World War I through the biological threats of the Cold War to the present day, defense against chemical and biological (CB) weapons has been a part of the US national security strategy. While advances in defensive technology have clearly improved, some capabilities have not changed markedly in nearly 20 years and a few that have changed very little in 60 years or more.

The last decade, however, has brought an intersection of two key drivers that require a completely new way to look at CB defense and the challenges of CB proliferation. The first, the changing nature of the threat to the USA and its allies began with the fall of the Soviet Union and was magnified greatly by the events of September 11, 2001. Second is the shifting nature of technological progress that brings entirely new capabilities, many of which are no longer the exclusive domain of the USA. These drivers – ranging from the depth of biological research in the former Soviet Union to the rise of asymmetric attacks – offer new opportunities and new challenges for CB defense.

Understanding these changing paradigms and limiting the proliferation of CB weapons that may be based on nanotechnology starts with an awareness of the following:

- The definition and potential applications of nanotechnology;
- Factors driving the capabilities, underlying science and challenges of CB defense: the changing nature of technological progress, the changing nature of warfare, the relationship between science and national security, and the underlying needs of the individual warfighter and the overall military; and
- The evolution of federal guidance on CB defense and the government's organization of CB defense resources.

Responding to a New Threat Environment

The rapid diffusion of technology, the growth of a multitude of transnational factors, and the consequences of increasing globalization and economic interdependence, have coalesced to create national security challenges remarkable for their complexity.

– General Charles C. Krulak, 1999¹

In the rapidly changing post-Cold War environment, the most technologically advanced military power no longer guarantees national security. Globalization and the information revolution have made new technological developments accessible and relatively inexpensive to many nations and within the grasp of individuals or groups with malicious purposes, referred to as nonstate actors. Advanced technology is no longer the domain of the few.² In the twenty-first century, both nation-states and nonstate actors may have access to new and potentially devastating dual-use technology.³ Nanotechnology is one such technology that could have dual uses.⁴

Recent advances in biotechnology and information technology have been driven by needs for improved biomedical products, public health, or industrial applications. In some cases, negative or undesirable results from existing experimental data may be harnessed to develop potential weapons. For example, when toxicity screens are performed, the success of the experimental design is considered according to the ability to differentially kill certain cells over others. The “negative data” or undesirable effects that kill healthy cells, however, may provide the seeds for adversaries to identify develop new unforeseen weapons. The same is true for data derived from nanomaterial experimentation. For these reasons, the entire data set should be considered valuable. Such results, combined with the wide availability of information via the internet, have also fostered the proliferation of known CB agents and spurred interest in the creation of novel nontraditional agents.⁵

The Changing Nature of Warfare

Much of our government and interagency [programs and program managers] seem to be in a state of denial about the requirements needed to adapt to modern warfare.

— Lieutenant General Peter W. Chiarelli, 2007⁶

During the Cold War, the United States and its allies was able to focus national security efforts on a single enemy and on a single type of war. That situation no longer exists. Enemies of the US and its allies in the next 20 years are likely to be less focused on strategies for “world domination” using known stockpiles of nuclear, chemical, or biological weapons to focus on ways to deter US action, deny access, and preempt operations. Anonymous, nonattributable attacks may be aimed at disrupting regional stability, and all of this will impact ongoing nonproliferation, counterproliferation, international development, and economic efforts.

While possessing tremendous variation throughout history, nonstate actors (including terrorists) have tended to be more tactically oriented, in the desire both to possess and use nontraditional or unconventional weapons and to disrupt economic and symbolic targets. They are difficult to locate, monitor, and target, and have the ability to quickly make and use weapons from benign precursors. They are able to attack targets without warning or attribution, and these targets may be irregular,

such as food, water, and agriculture. Attacks against the civilian populace are more likely and more commonplace. Through all of this, states continue to mainly operate in traditional ways, causing a disconnect between attacks by terrorists and state-based preparations for defending against them.

International and domestic terrorists have clearly demonstrated the intent to obtain, develop, and use CB materials as weapons. As the leader of a larger radical Islamist movement, Al Qa'eda has advocated the use of terrorism to cause the economic collapse in the US and the Western world. The exploits of Al Qa'eda in Afghanistan to test unspecified lethal chemical agents on animals have been well-covered in the news media.⁷ Additional evidence and analysis of Al Qa'eda's extensive interest in chemical agents was highlighted in a 2005 Intelligence Commission report.⁸ The recovered tactical manual, *Muswatul Jihad al-Afghani (The Encyclopedia of Jihad)*, contains 11 volumes detailing development and concepts of terrorist operations for chemical agents and explosives. Another radical Islamic group, Ansar al-Islam in northern Iraq, was reportedly developing cyanide-based chemical agents in 2002.⁹ In the 1990s, the Japanese cult, the Aum Shinrikyo, employed hydrogen cyanide, VX nerve agent, and sarin nerve agent against civilians and unsuccessfully attempted to develop and use *Bacillus anthracis*, the causative agent of anthrax.

Domestic terrorist groups, including right-wing antigovernment groups and affiliates of government laboratories, have sought, planned, obtained, and intended to use biological and chemical agents.¹⁰ Use of biological material such as *Salmonella* bacteria by the Rajneeshees in The Dalles, Oregon in 1984 and the *B. anthracis* "Amerithrax" sent through the US postal system in 2001 are two examples of domestic terrorism in which US-developed technologies were used to deploy biological agents. The Rajneeshees used an unsophisticated, improvised technique by sprinkling material on a local salad bar. Although the Amerithrax underwent fairly sophisticated processing, distribution in envelopes sent through the mail was also improvised and unsophisticated. These cases demonstrate that research laboratories of all types may be subverted by overtly harmless people with malicious intent.

Other major changes are in military strategy. Examples include the emphasis on transformation within the DoD and the elevation of stability, security, transition, and reconstruction (SSTR) operations to the same level as traditional combat operations¹¹ coupled with the increased emphasis on counterinsurgency strategy¹² and unconventional warfare.¹³ Within traditional military operations, combat operations ended with a signed armistice or treaty of surrender, and then SSTR began, for example, activities in Germany and Japan following World War II. With counterinsurgency operations, there is no formal end of combat operations, and therefore no distinct linear transition. Over the last hundred years, the defense community in the US, with few exceptions,^{14,15} has historically relegated consideration of the nature and requirements of counterinsurgency, unconventional warfare, and stability operations a distant second or third to traditional "high-intensity" conventional combat operations and peer-on-peer competitors.¹⁶

It is not readily apparent how the CB defense research and development community are addressing these changing requirements of the warfighter in stability

operations. It is unclear what the role is for the science and technology in enabling stability operations, unconventional warfare situations, and moving away from focus on Cold War adversaries. These paradigm shifts highlight the need for innovation in countermeasures against threats from chemical, biological, nuclear, and radiological materials, in addition to improvised and high explosives.

The Changing Nature of Technological Progress

Technology is accelerating at an unprecedented pace. Advances in information technology, for example, have led to a world almost completely connected with microchips and unparalleled global interconnectivity by which tremendous quantities of information can be shared at unprecedented speeds in human history. At the same time, advances in biotechnology have permeated everyday life from new drugs to DNA research that is beginning to unlock the secrets of human behavior through the neurosciences and the cognitive sciences. These advances have had dramatic effects on defense and are made complex by a number of independent and dependent factors.

Globalization as a Driver

Changes in technology can most easily be seen as a decrease in the cost and increase in the availability of technology, tools, and materials. As technologies become more inexpensive, they become more widespread and available. Along with this is the dissemination of the expertise of breakthrough science. Once the domain of well-funded entities such as research universities, large federal laboratories, and a few state governments technology developments – particularly in niche areas – can now originate globally and are equally likely to be funded by transnational corporate entities, small firms or venture capital as by traditional means.

Global integration through advances in information and communications technology is another crystallizing factor. The internet and other communication leaps have led to much greater visibility into the availability and potential for technology.¹⁷ This transparency and ease of access to a global knowledge base can lead to greater stability for states but also can empower individuals. In today's world, people spread across the globe connect quickly and cheaply. Increased economic interdependence and increased interconnections between states can lead to greater cooperation and improved diplomacy. The concept that growth in free trade and economic interdependence will lead to fewer conflicts remains a question. This improved transparency, however, into international technology development is likely to decrease state-sponsored CB weapons development within the integrated global community.

Global energy distribution and demand is a major factor in overall stabilization of the world economy. Disparity of energy access can drive conflict; moreover, as traditional energy sources become less accessible, more pressure is placed on technology to find alternatives.¹⁸ This affects states more than individuals.¹⁹

Sociopolitical instability is a factor that can impede technology progress. States with high levels of social conflict dedicate fewer funds, fewer people, and fewer institutions to technology progress. States in this situation are less likely to develop CB threats; however, they are more likely to harbor nonstate actors who will try to do so. In addition, many places in the world have a socioreligious motivation to decrease funding for new science and technology, preferring to live in what is perceived or professed as a simpler time.

Revolutionary Technology on the Nanoscale

Those countries that master the process of nanoscale manufacturing and engineering will have a huge job boom over the next 20 years, just like aviation and computing companies in the last 40 years, and just as railroad, steam engine and textile companies were decisive in the 19th century. Nanoscale science will give us not dozens, not scores, not hundreds, but thousands of new capabilities in biology, physics, chemistry and computing.

– Former Speaker of the House Newt Gingrich, 2002²⁰

Technology advances enabled by nanoscience, though less recognized than information science and biotechnology, are a major driver in advances in emerging sciences. Nanotechnology, encompassing a broad spectrum of nanoscale science and engineering, can be described as an array of fundamental knowledge and enabling technologies resulting from efforts to understand and control the properties and function of matter at the nanoscale.²¹ The term nanotechnology also labels a vision first described by Richard Feynman in his classic talk, “There’s plenty of room at the bottom,” where he outlined the potential for new fundamental work at the nanoscale.²² The concept – and the terminology – was popularized by K. Eric Drexler during the 1980s and 1990s.²³

Figure 1.1 depicts how this scale relates to natural and man-made objects. For instance, DNA, cells, atoms, and light are of this size. At the nanoscale, phenomena are no longer dominated by bulk properties. Chemists and biologists routinely deal with these small building blocks. A single water molecule is approximately one-tenth of a nanometer wide at its widest; hemoglobin – the globular protein responsible for carrying oxygen from the lungs to the body’s tissues – is 5 nm in diameter. The length scale of biochemical process inside the cells is at the nanoscale. Nerve transmissions, synaptic junctions between nerve cells in the brain (20–40 nm) and nerve cells and muscles (3–4 nm), are nanodimensional. More recently, scientists and researchers are exploiting the nanoscale outside the biological realm. For example, friction and surface energy are fundamentally different at the atomic level,²⁴ and working at this scale is yielding new understanding and capabilities of catalysis and other surface-driven properties. Photonic crystals are built on this scale in order to provide unique interactions with the nanometer wavelengths of light. Quantum wells are another example of the use of nanoscale to create entirely new phenomena.

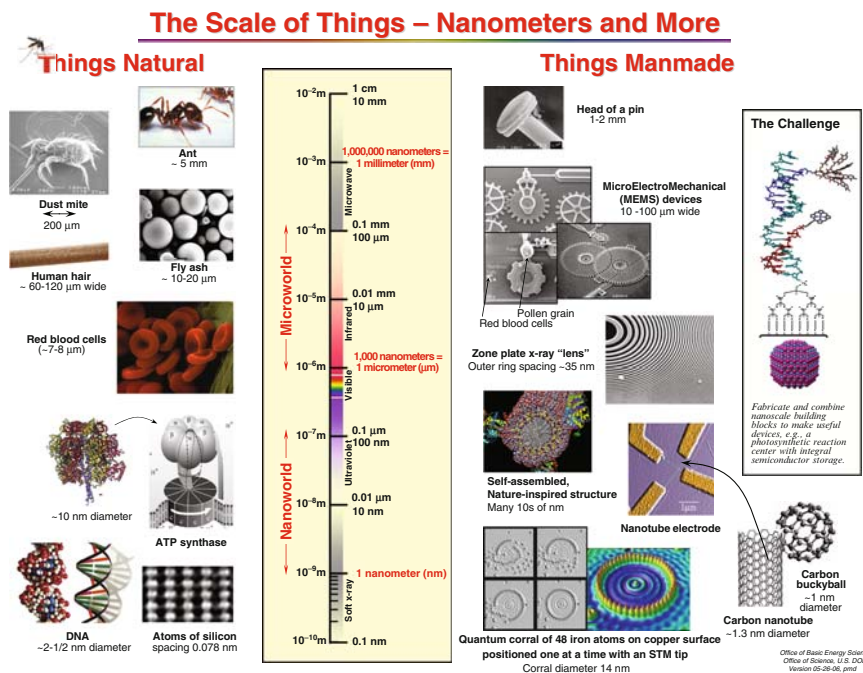


Fig. 1.1 Overview of natural and synthetic nanoscale materials in context of micro- and macroworld, as well as the atomic scale. Source: Department of Energy Office of Basic Energy Sciences. Detailed figure available at http://www.sc.doe.gov/bes/scale_of_things.html

Among the first popular descriptions of “nanotechnology” were nanomachines capable of assembling themselves, whether spontaneously or via some designated signal. Today, the meaning and application of nanotechnology is much wider. Nanotechnology is not a specific determinate homogenous entity but is perhaps better described as a collection of diverse capabilities, with expectations of synergies among them. Multiple terms are used to describe and name the fields associated with nanotechnology: nanoscience, nanoengineering, nanoengineered materials, bionanotechnology, supramolecular science, and self-assembly.

From Science to Application

These visions of nanotechnology and related investments are now coming to practical fruition. Innovations in pharmacological formulations, contrast agents for biomedical imaging, fabrics, optical materials, and superstrong protective coatings are examples. Engineered nanoparticles are currently used in a number of commercial products,

including cosmetics, clothes, sunscreens, and electronics.²⁵ In medicine, nanotechnology is expected to impact medical diagnostics, drug delivery systems, therapeutics, and vaccines.²⁶ Applications for all of these are in varying stages of transition from research to the marketplace. A variety of unique properties imbued into substances on the nanoscale are being integrated into commercial technology and defense products.

International Investments in Nanotechnology

Twenty-first century nanotechnology investment intrinsically traverses national borders. In 2002, the European Union committed \$3.3 billion over the subsequent 2 years and is now estimated to be investing €1 billion per year.²⁷ In 2001, Japan identified nanotechnology as a main research priority²⁸ and subsequently has increased its investment to exceed \$1 billion per year for nanotechnology research. China views itself as a leading global contributor²⁹ and is putting an estimated \$300–400 million per year toward nanotechnology research.³⁰ South Korea and Taiwan also have robust, federally funded nanotechnology programs.³¹ While funding numbers are not available, Iran has a nanotechnology strategy that is similar to the US National Nanotechnology Initiative (NNI),³² including a nanotechnology coordinating office.³³

In April 2007, Russia's President, Vladimir Putin, announced plans to invest almost 28 billion rubles between 2008 and 2010 in nanotechnology as part of an intensive effort to make Russia a leading global competitor in nanotechnology. In June 2007, the creation of a state nanotechnology corporation, Rosnanotekh, was announced along with \$5 billion in initial funding. Some have asserted that such an investment will push Russia ahead of China in nanotechnology spending and into a comparable position to the USA. Striking in its similarity to the US NNI, Russia's network of institutes and research center for nanotechnology is known as the "NNN." The Russian Science and Education ministry has drafted a nanotechnology development program through 2015.

The designers of the Russian nanotechnology initiative notably have both military and civilian applications in mind. Former Russian President Putin has noted that nanotechnology is already being used in high-tech sectors of industry, medicine, transport, space research, and telecommunications, while suggesting that nanotechnology will enable new offensive and defensive weapons systems.³⁴ Putin has emphasized the connections between the overall national economy, technological advancement through nanoscience, and military applications: "Russia's economic potential has been restored, and the possibilities for major scientific research are opening up. The concentration of our resources should stimulate the development of new technologies in our country. This will be key also from the point of view of the creation the newest, modern, and supereffective weapons systems."³⁵ During a visit to the Kurchatov Institute, Putin commented "This could be the key to developing new, modern, and effective military systems. Nanotechnology is an activity for

which this government will not spare money.”³⁶ It is not clear to what extent Russia has the technical or infrastructure capabilities to realize such goals.

Unintended Consequences

Military applications of molecular manufacturing have even greater potential than nuclear weapons to radically change the balance of power.

– Former Vice Chairman of Joint Chiefs of Staff Admiral David E. Jeremiah (ret), 1999³⁷

Although the potential threats of nanotechnology research in an age of terrorism or a new age of state-based proliferation may not be as easy to envision in the near term as those associated with biotechnology, the possibilities are becoming more real as nanotechnology is transitioned from the laboratory to products. A number of recent advances in nanotechnology have made clear nanotechnology’s malfeasant potential in the hands of adversaries. The inability of traditional CB technologies to provide technical solutions to the threats facing the US and allies indicate that nanotechnology will have a significant impact on CB defense in the twenty-first century. As such, the time has come to construct a coordinated federal plan to prepare for and to consider the international security implications related emerging threats.

Currently, science-based evidence is used primarily to underpin domestic regulations on nanotechnology, with goals to prevent unintended environmental, safety, and health consequences. A number of regulatory guidelines put forth by the Environmental Protection Agency, the National Institute for Occupational Safety and Health, or the Food and Drug Administration, however, do not address consequences to national security. Additional complexities arise when these goals intersect; for example, when the DoD relies on the FDA to approve medical countermeasures.

Internationally, two key arms control treaties pertain to proliferation of nanotechnology-enabled biological and chemical weapons: the Biological and Toxin Weapons Convention (BWC) and the Chemical Weapons Convention (CWC). These international agreements apply explicitly to traditional biological and chemical weapons. The CWC extends to nanoenabled weapons with similar purposes hypothetically. In particular, Article I of the CWC contains a general purpose criterion that prohibits use, development, production, stockpiling, and transfer of toxic chemicals and their precursors, as well as munitions and devices, specifically designed to cause death or other harm through the toxic properties of any chemical agent. The intent of the general purpose criterion was to allow the CWC to remain relevant as new technological developments might arise and, in the case of dual-use chemicals, to exempt application for peaceful purposes from its prohibitions.

Reducing the risk from state-based misuse of nanotechnology for biological or chemical weapons will mean consideration of the highly transnational nature of nanotechnology research and development. Traditional and innovative new approaches to nonproliferation and counterproliferation are important policy elements to reduce the risk of malfeasant application of nanotechnology. Robust international agreements lower the risk of terrorist applications by eliminating legal routes for

terrorists to obtain chemical agents, precursors, or weaponization materials, and by minimizing transfers from state to nonstate actors through theft, deception, or other means. Efforts to strengthen the international regime to control transfers of dual-use chemicals are also important. Currently, the limited number of security-oriented studies that have considered nanotechnology have largely turned to existing models, such as implementing a new “arms control treaty” for nanotechnology.^{38–40} Others have proposed extending current federal biosecurity models, such as a “code of conduct” for nanoscientists.⁴¹ Some nongovernmental organizations have also advocated the imposition of the precautionary principle across many aspects of nanotechnology.⁴²

Nanotechnology is not the first revolutionary science development that raises fears of unintended consequences in this way. Over the last 35 years, biotechnology has resulted in a number of voluntary and regulatory actions to address the safety and security risks associated with cutting-edge research and publication of research findings. The science^{43,44} and intelligence^{45,46} communities are currently attempting to develop new means to address security risks. From the genetic engineering of a supervirulent strain of mouse pox to the synthesis of artificial polio virus, the potential misuse of molecular biology for biological weapons has received much attention both in the popular press and within the academia. As similar concerns are raised for nanotechnology, successes in biotechnology, while they may be limited tools in a larger metaphorical tool box, provide valuable lessons.

Other Critical Factors

As described above, the pace of change/development of technology will greatly affect the development of nanotechnology in the CB defense. Additionally, there are overarching external factors to consider as part of this exploration. The first is that no matter how interesting or useful a technology appears, it does not have value unless it is implemented in the context of the mission, whether traditional military defense, homeland security, or within counterproliferation, counterterrorism, or counterinsurgency operations. Technology must be useful to operators. Second, there is an interaction among science, technology, and national security that provides research capability to the US and allies and, unfortunately, to the adversary. Finally, the effectiveness of any effort is enhanced or limited by the surrounding organizational structure.

Underlying Needs of the Operator

The technology itself must be translated into weapons that are effective in actual combat. At present, our research, development, and procurement process has great difficulty making this transition. It often produces weapons that incorporate high technology irrelevant in combat or too complex to work in the chaos of combat... The current American research, development, and procurement process may simply not be able to make the transition to a militarily effective fourth generation of weapons.

The expeditionary warfighter, the homeland defender, and the first responder will ultimately be in the position to use the resulting technological advances. Nanotechnology and nanotechnologically enabled or – enhanced materials and tools offer promise for substantive increases in effectiveness, convenience, and protection to users. Like any technology, the advantages will have to be balanced with the primacy of the mission and the practical needs of operators to have easy to use application that do not require complicated instructions or training.

While many of the military officers who serve in leadership capacities in operational units have technical training, few are knowledgeable about the promise of nanotechnology. Many recognize the potential, however, and by providing perspectives on the application of nanotechnology, active duty and retired operators can ground the development of scenarios and strategic research priorities in real warrior requirements.⁴⁸

Operators express concern that new technology requires too much training, requires too much maintenance, are too delicate, are too expensive, and perhaps most importantly, may “let you down when you need it the most.” As training requirements increase, the value of new technology is seen to rapidly decrease, due to the rapid turnover of personnel and the burden of off-site training on the mission. Any additional training required for maintenance is also a detractor from new technology. The need to literally “keep it simple” is repeatedly stressed with respect to the introduction of new equipment or instrumentation. The underlying technology may be fantastically complex, but the focus needs to be on usability for the operator.

The nature of the operational space – whether traditional battlefield, urban insurgency, or domestic city – also requires new technologies be made rugged to endure the harsh operational environments. Products must be customized (or customizable) for the requirements of the operators and their setting. Requirements for an effective product include that it work reliably in mud, dust, ice, heat, toxic, or caustic environments. Tools must also have tolerance for shock and should be able to survive decontamination processes. Ideally, devices are reusable with few or no consumables, are easily man portable, and, of course, are cost-effective. These requirements not only aid the operators in completing their mission but better ensure their survivability.

Relationship Between Science and National Security

Looking towards the future, the science and engineering workforce issue is probably our number one national security issue...we have to be concerned at the number of very smart people showing up in so many other places

–John H. Hopps, Deputy Under Secretary of Defense, 2004⁴⁹

Scientific and technological innovations have been the backbone of American economic, military, and political power since the advent of the industrial revolution. Federal support for research and development was invigorated by the arguments

and evidence put forth in Vannevar Bush's now-famous report to the President in July 1945.⁵⁰ At that time, the revolutionary power and security implications of research-driven development of the atomic bomb were palpable to American policy makers, the civilian leadership in the Department of War, and the armed forces. Advances in federally sponsored technology made the US and its armed forces the most technologically advanced in the world.

For strategists and scholars of revolution in military affairs^{51,52} and of fifth generation warfare,⁵³ the nexus between technology and military is not just a speculation but a reality that has often determined the outcome of war and been the critical variable in international security: military research and technological advances are intricately tied. Within today's most cutting-edge scientific and technological innovations – nanotechnology, biotechnology, and the cognitive sciences – is emerging research cited as carrying the potential of bringing the future envisioned in many utopian and dystopian scientific fictions closer.

Winning in an asymmetric warfare regime requires more than traditional technological superiority – it requires innovative and revolutionary technologies. In 2006, the Defense Science Board (DSB) was charged with looking back to the Cold War and the technologies and concurrent capabilities – precision, speed, stealth, and tactical intelligence, surveillance, and reconnaissance – that gave the US a technological advantage over adversaries and identifying equivalent technological capabilities for the twenty-first century.⁵⁴ They concluded that technological superiority is a strategic differentiator for the US. As a result of evolving conditions, the US cannot assume that it will stay ahead of its adversaries by simply spending more on research, development, and procurement.

The DSB report also concluded that the global environment in which the DoD operates had fundamentally changed, and that the DoD no longer solely leads most technology development. Globalization of technology has leveled the playing field internationally and the US faces more complex security challenges than at any time in its past. Additionally, adversaries are increasing their ability to adopt and adapt technology more rapidly than the DoD. The changing global environment requires the DoD to carefully evaluate, shape its programs in response, and be willing to take risks.

The 2006 Quadrennial Defense Review (QDR) noted that sustaining America's scientific and technological advantages over any potential competitor contributes to the nation's ability to dissuade future forms of military competition, including CB agents.⁵⁵ While human capital is essential for the DoD to realize the technology needed to dominate over adversaries of the twenty-first century, the lack of career science and technology development may become a crisis that extends to all DoD activities. This is exacerbated by the national decline in math and science education, and together these create the national security challenge decried in a prominent National Academy of Sciences report entitled, "Rising Above the Gathering Storm."⁵⁶ This report recognized that science education, jobs, and innovation are closely connected. This point was reemphasized in the American Competitiveness Initiative, which also called out the importance of entrepreneurship and innovation to national security.

In the changing global strategic environment, the US no longer has an exclusive or exclusively dominant position in the research and development of emerging technologies. In some cases, the research community has chosen – through resource allocations – to fund some areas only for a short time, others for many years, with a constant eye on “requirements pull” versus “technology push” and the need to balance the two. This is exemplified in the financial world by the concept of “hedging,” where an investor chooses to invest in some securities that are expected to gain more and some that are expected to gain less (or lose) in order to minimize risk. Thus, the hedger is indifferent to the movements of the market as a whole, and is interested only in the performance of the potentially poorer investments relative to the hedge. When the federal research investment “hedges” in this way, the potential for substantial scientific gain decreases dramatically. Only by making strategic choices and by reevaluating and reinvesting as new technologies emerge, real gains can be made.

It is important to consider whether the implicit hedging strategy actually protects against risk in an environment in which the US role as the global technology leader may be challenged and in which an ever increasing number of participants enter the global R&D market. In such an environment, one strategy choice may be for the US to pursue and obtain the absolute lead in a few critical areas and – through hedging – develop secondary or lower roles in other areas. Uncertainty prognoses warrant a hedging strategy in some areas, yet the asymmetric nature of the threat warrants dominant leadership in others. Although no level of investment guarantees success, it has become clear that nanotechnology is a research area in which the US should not hedge.

Evolving Federal Guidance

How the Federal government organizes and manages the execution of science and technology components of CB defense programs is an additional driver for and impact on research and development. Understanding this organization begins with an examination of the guidance under which the US operates and the agencies that administer funding and deployment of new technologies.

In 2000, President Bill Clinton advocated nanotechnology development, and President George W. Bush further increased funding for nanotechnology during his tenure. Within the US military, defense community, and homeland security, nanotechnology research finds many proponents.^{57,58} The Defense Department has traditionally funded only one-quarter to one-third of the US federal R&D in nanotechnology.⁵⁹ In 2008 and 2009, the DoD exceeded the National Science Foundation in nanotechnology-related research and development funding.⁶⁰ The vast majority of DoD-funded research is basic research without any specific application in mind or done with defensive applications in mind.

In all federally funded research, in addition to domestic laws and regulations, the US remains committed to international treaties on prohibition of CB weapons. As

State party to the BWC, the US does not conduct offensive biological research.⁶¹ As a State party to the CWC, the US does not conduct offensive chemical research.⁶²

Executive Agency Directives

We aim to convince our adversaries that they cannot achieve their goals with [weapons of mass destruction], and thus deter and dissuade them from attempting to use or even acquire these weapons in the first place.

– National Security Strategy of the USA, 2006⁶³

The Federal programmatic context for CB defense has changed dramatically in recent years. This is reflected in a number of national and military strategy documents that guide US CB defense efforts. Each of these documents attempts to direct programs that respond to the changing threat environment. The most relevant national strategy documents are described below.

The national strategy on CB defense encompasses several primary directives. The President's *National Security Strategy* states that countering the spread of biological and chemical weapons will require a strategy encompassing detection, response, and mitigation, both abroad and at home.⁶⁴ This directive also cites the critical goal to develop and integrate countermeasures to CB weapons into defense transformation as the DoD adjusts to meet the new demands of SSSTR operations. Additionally, US forces are directed to actively seek to prevent the use and proliferation of CB weapon technology to irresponsible nations and nonstate actors. The Nation's comprehensive strategy to combat weapons of mass destruction includes identifying proactive counterproliferation efforts, impeding weapons and materiel proliferation with diplomacy and interdict when necessary, and enhancing consequence management.

Biodefense in the 21st Century is a White House directive that integrates the sustained efforts of the national and homeland security, medical, public health, intelligence, diplomatic, and law enforcement communities.⁶⁵ The four pillars of the biodefense program as described are threat awareness, prevention and protection, surveillance and detection, and response and recovery. The latter two pillars speak to the need for improved capabilities in the areas of surveillance, specifically detection and diagnostics, as well as medical countermeasures development and decontamination.

The President's *National Strategy to Combat Weapons of Mass Destruction*⁶⁶ states, "The gravest danger our nation faces lies at the crossroads of radicalism and technology." This expands on the National Strategy of *Counterproliferation, Nonproliferation, and Consequence Management* and describes the need to integrate the pillars described above. Further, it emphasizes the "four Ds": *defeat* terrorist organizations, *deny* further terrorist sponsorship, *diminish* conditions causing terror, and *defend* using proactive actions.

With regard to the Defense Department, the *US National Defense Strategy* goes into more detail than the *US National Security Strategy*, setting priorities and objectives

for the DoD, which then link military activities to those of other government agencies. The *National Military Strategy*⁶⁷ implements the objectives of the National Defense Strategy. CB defense falls under several areas in the *National Military Strategy to Combat Weapons of Mass Destruction*,⁶⁸ most notably interdiction operations and consequence management.

As an examination of military strategies, the 2006 QDR echoes and builds upon other military strategy documents. An overarching principle of these strategies is an admission that the security environment of 2025 cannot be accurately characterized, and that identifying and developing a broad range of capabilities is a hedge against the uncertainty. The QDR recommended the DoD go “from twentieth century process to twenty-first century integrated approaches.”⁶⁹ To do so, DoD transformation will need to respond to a shift in the strategic environment to an era of surprise and uncertainty.

Previous DoD strategies have centered on known threats and well-described if multiple, complex challenges. The QDR encouraged a change to capabilities-based planning and a shift from crisis response to rapid adaptive preparation. The document aims to serve as a catalyst to spur continuing adaptation and reorientation to produce an integrated joint force that is more agile, more rapidly deployable, and more capable against the wider range of threats.

Since its inception in 2003, the Department of Homeland Security has also been a major actor in CB defense. *The National Strategy for Homeland Security* and *Securing Our Homeland: The 2004 DHS Strategic Plan* both contain significant recommendations on CB defense research. Areas of focus in the National Strategy for Homeland Security include detecting CB materials and attacks, improving chemical sensors and decontamination techniques, and harnessing the scientific knowledge and tools to counter terrorism.⁷⁰

Securing Our Homeland emphasizes capabilities development and also reliance on “the vast resources and expertise from the Federal Government, private sector, academic community, nongovernmental organizations, and other scientific bodies.”⁷¹ A crosscutting theme of all of these strategies is increased emphasis on interagency coordination.

Defense strategies for CB threats across the government emphasize the same overall issues; the individual programs, however, vary in size and scope. Prior to September 11, the DoD investment in CB defense comprised nearly the entire federal outlay in CB countermeasure development. In the ensuing years, the scope of programs has widened. Currently, the DoD investment represents about one-quarter of the total investment of more than \$6 billion.⁷² DoD’s most notable efforts are within the CBDP and at DARPA. This budget also has significant efforts at the Department of Health and Human Services and the Department of Homeland Security and more targeted contributions from the Department of Energy, the Environmental Protection Agency, the Department of State, and the Department of Commerce. These agencies work in informal coordination.

Significant interagency interactions occur across CB defense research ranging from informal to formal coordination. Specific coordination in nanotechnology for

CB defense is less common. A short overview of the major programs in Appendix A describes the breadth of the federal investment.

Notes and References

1. Krulak CC (1999) The strategic corporal: Leadership in the three block war. Marine Magazine. http://www.au.af.mil/au/awc/awcgate/usmc/strategic_corporal.htm Accessed 30 June 2008.
2. Office of the Director of National Defense (2007) Unclassified key judgments of the national intelligence estimate, prospects for Iraq's stability: A challenging road ahead. <http://www.dni.gov>. Accessed 30 June 2008
3. National Research Council (2006) Globalization, Biosecurity, and the Future of the Life Sciences. National Academies Press, Washington DC.
4. Within this text, the dual-use and the dual-use conundrum refers to the fact that almost all the equipment and materials needed to develop dangerous or offensive agents, particularly biological and chemical agents, have legitimate uses in a wide range of scientific research and industrial activity, including defensive military uses. Within this text, it does not refer to the demarcation between civilian and military uses.
5. National Research Council (2004) Biotechnology Research in an Age of Terrorism. National Academies Press. <http://fermat.nap.edu/books/0309089778/html/>. Accessed 30 June 2008
6. Chiarelli PW, Smith SM (2007) Learning from our modern wars: The imperatives of preparing for a dangerous future. *Mil. Rev.* 2–15
7. Dana Priest "Archive of Al Qaeda Videotapes Broadcast; Dogs Shown Dying from Toxic Vapor," The Washington Post, 21 August 2002, p. A13.
8. Report to the president (unclassified) (2005) Commission on the Intelligence Capabilities of the United States Regarding Weapons of Mass Destruction. <http://www.wmd.gov/report/index.html>. Accessed 30 June 2008
9. US Senate Report on Pre-War Intelligence on Iraq (2006) Select Committee on Intelligence. <http://intelligence.senate.gov/phaseiiaccuracy.pdf> Accessed 30 June 2008.
10. Tucker JB (2000) Toxic Terror: Assessing Terrorist Use of Chemical and Biological Weapons. MIT Press, Cambridge.
11. Department of Defense Directive 3000.05 (2005) Military Support for Stability, Security, Transition and Reconstruction (SSTR) Operations. Issued on 28 November.
12. US Army Field Manual (2006) Insurgency FM 3–24. <http://usacac.army.mil/CAC/Repository/Materials/COIN-FM 3-24.pdf> Accessed 30 June 2008.
13. Joint publication 3–05: Doctrine for joint special operations (2003) http://www.dtic.mil/doctrine/jel/new_pubs/jp3_05.pdf Joint Chiefs of Staff. Accessed 30 June 2008.
14. Kelley RE (2000) US Army special forces unconventional warfare doctrine: Engine of change or relic of the past?. U.S. Naval War College. <http://handle.dtic.mil/100.2/ADA378713> Accessed 30 June 2008.
15. Metz S and Millen R (2004) Insurgency and counterinsurgency in the 21st century: Reconceptualizing threat & response. Strategic Studies Institute. <http://www.strategicstudies-institute.army.mil/pdf/PUB586.pdf> Accessed 30 June 2008.
16. Ucko D (2008) Innovation or inertia: The U.S. military and the learning of counterinsurgency. *Orb.* 52:2.
17. Rennstich JK (2008) The making of a digital world: The evolution of technological change and how it shaped our world. Palgrave MacMillan, New York.
18. National security and threat of climate change. CNA (2007) http://securityandclimate.cna.org/report/SecurityandClimate_Final.pdf. Accessed 30 June 2008.
19. Mapping the global future: Report of the national intelligence council's 2020 project NIC 2004-13. Government Printing Office # 041-015-00240-6 (2004). <http://www.foia.cia.gov/2020/2020.pdf>. Accessed 30 June 2008.

20. Josh Wolfe "Decoding Future Nanotech Investment Success," *Forbes/Wolfe Nanotech Report*, 10 October 2002.
21. National Research Council (2006) A Matter of Size: Triennial Review of the National Nanotechnology Initiative. National Academies Press, Washington, DC.
22. Feynman R (1959) There's plenty of room at the bottom: An invitation to enter a new field of physics. Zyvox. <http://www.zyvox.com/nanotech/feynman.html> Accessed 30 June 2008.
23. Drexler KE (1981) Molecular engineering: An approach to time development of general capabilities for molecular manipulation. *Proc. Natl. Acad. Sci. (PNAS)* 78:5275–5278.
24. Purcell EM (1977) Life at low Reynolds number. *Am. J. Phys.* 45:3–11.
25. National Research Council (2006) A Matter of Size: Triennial Review of the National Nanotechnology Initiative. Washington, DC., National Academies Press.
26. Zhang S (2003) Fabrication of novel biomaterials through molecular self-assembly. *Nat. Biotech.* 21:1171–1178. http://web.mit.edu/lms/www/PDFpapers/Zhang_NatureBio78D70.pdf Accessed June 30 2008.
27. European Union (2004) Towards a European strategy for nanotechnology. http://ec.europa.eu/nanotechnology/pdf/nano_com_en_new.pdf Accessed 30 June 2008.
28. Government of Japan (2001) Japan 2nd S&T Plan (2001–2005). http://www8.cao.go.jp/cstp/english/basic/2nd-BasicPlan_01–05.html Accessed 30 June 2008.
29. Bai C (2005) Ascent of nanoscience in China. *Science*. 309: 61–63. <http://www.sciencemag.org/cgi/content/full/309/5731/61> Accessed June 30 2008.
30. Appelbaum RP, Gereffi G, Parker R et al (2006) From cheap labor to high-tech leadership: Will China's investment in nanotechnology pay off?. *Constituting Globalization: Actors, Arenas, and Outcomes*. http://www.cggc.duke.edu/pdfs/workshop/Appelbaum%20et%20al_SASE%202006_China%20nanotech_27%20June%202006.pdf Accessed 30 June 2008.
31. Hariharan K (2005) Governments lead the charge for nano's development in Asia. *Small Times*. http://www.smalltimes.com/articles/article_display.cfm?Section=ARCHI&C=RD&ARTICLE_ID=270161&p=109 Accessed 30 June 2008.
32. Iranian Nanotechnology Initiative (<http://www.nano.ir/>, English language site: <http://nano.ir/en/>), Islamic Republic News Agency "President Calls for Setting up of National Nanotechnology Organ" 15 July 2006 (<http://www.irna.ir/en/news/view/menu-236/0607158657171656.htm>).
33. Nanotechnology Policy Studies Committee, Available at <http://www.tco.ac.ir/nano/>
34. RIA Novosti (2007) Putin vows to bankroll nanotechnology, stresses payoff. <http://en.rian.ru/russia/20070418/63882148.html> Accessed 30 June 2008.
35. Associate Press (2007) Russia to invest over US\$1 billion in nanotechnology in next three years. *International Herald Tribune*. <http://www.iht.com/articles/ap/2007/04/18/technology/EU-TEC-Russia-Nanotechnology.php> Accessed 30 June 2008.
36. Reuters (2007) Putin promotes nanotechnology in Russia. <http://www.javno.com/en/economy/clanak.php?id=36370> Accessed 30 June 2008.
37. "Nanotechnology and Global Security," (Palo Alto, CA; Fourth Foresight Conference on Molecular Nanotechnology), 9 November 1995.
38. Howard S (2002) Nanotechnology and mass destruction: The need for an inner space treaty. *Disarm. Dipl.* 65.
39. Altmann J (2004) Military uses of nanotechnology: Perspectives and concerns. *Secur. Dialogue* 35:61–79.
40. Pardo-Guerra, Pablo J, Aguayo AF (2005) Nanotechnology and the international regime on chemical and biological weapons. *Nanotechnology, Law & Business* 2:1.
41. Break-out group discussion on the potential for misuses of nanotechnology, held at the Workshop on Ethical Aspects of Nanotechnology, January 11–12, 2007, Arizona State University, Tempe.
42. Raffensberger C and Tickner J (eds.) (1999) *Protecting Public Health and the Environment: Implementing the Precautionary Principle*. Island Press, Washington, DC. The precautionary principle states that if the results of a research program might cause severe or irreversible harm to the public, in the absence of a scientific consensus that harm would not ensue, the burden of proof falls on those who advocate undertaking the research.

43. National Research Council (2004) *Biotechnology Research in an Age of Terrorism*. National Academies Press. <http://fermat.nap.edu/books/0309089778/html/> Accessed 30 June 2008.
44. National Research Council (2006) *Globalization, Biosecurity, and the Future of the Life Sciences*. National Academies Press, Washington DC.
45. Petro JB, Plasse TR, and McNulty JA (2003) *Biotechnology: Impact on biological warfare and biodefense*. *Biosecur. Bioterror.: Biodef. Strat., Pract. Sci.* 1–3:161–168.
46. Central Intelligence Agency (2003) *The darker bioweapons future*. <http://www.fas.org/irp/cia/product/bw1103.pdf> Accessed 30 June 2008.
47. Lind WS, Nightengale K, Schmitt JF et al. (1989) The changing face of war: Into the fourth generation. *Marine Corps Gazette*.
48. Colonel Barry Lowe, USA “A Warfighter’s Perspective on Possible Nanotechnology Applications for CBRNE/WMD Operations,” Commander Michael Penny, USN “Military Operator’s View for Marine Chemical and Biological Incident Response Force (CBIRF),” and Major General John Doesburg, USA (ret), “Bridging Science and Military Operations,” 30 January 2007, *Nanotechnology for Chemical and Biological Defense 2030 Workshop*, Santa Fe NM.
49. The Minerals Metals, & Materials Society (2004) *The journal talks with the U.S. Department of Defense’s John H Hopps Jr.* <http://www.tms.org/pubs/journals/JOM/0404/Hopps-0404.html> Accessed 30 June 2008.
50. Bush V (1945) *Science: The endless frontier*. United States Government Printing Office. <http://www.nsf.gov/od/lpa/nsf50/vbush1945.htm> Accessed 30 June 2008.
51. McKittrick J, Blackwell J, Littlepage F et al (1995) The revolution in military affairs. In: Schneider BR, Grinter LE (eds.) *Battlefield of the Future: 21st Century Warfare Issues*. Air University Press, Maxwell AFB.
52. Cohen EA (1996) A revolution in warfare. *Foreign Aff.* 75: 41.
53. Hammes TX, “Fourth Generation Warfare Evolves, Fifth Emerges,” *Milit. Rev.*, May–June 2007, <http://usacac.army.mil/CAC/milreview/English/MayJun07/Hammes.pdf> Accessed June 30, 2008.
54. Defense Science Board 2006 Summer Study on 21st Century Technology Vectors, February 2007, 4 volumes (http://www.acq.osd.mil/dsb/reports/2006-02-Summer_Study_Strategic_Tech_Vectors_Vol_I_Web.pdf and http://www.acq.osd.mil/dsb/reports/2006-02-Summer_Study_Strategic_Tech_Vectors_Vol_II_Web.pdf). Accessed June 30 2008.
55. US Department of Defense (2006) *Quadrennial Defense Review Report*. <http://www.defenselink.mil/qdr/report/Report20060203.pdf> Accessed 30 June 2008.
56. Committee on the Prospering in the Global Economy of the 21st Century (2007) *Rise above the gathering storm: Energizing and employing America for a brighter economic future*. National Academies Press. http://books.nap.edu/catalog.php?record_id=11463 Accessed 30 June 2008.
57. Peterson JL and Egan DM (2002) Small security: Nanotechnology and future defense. *Def. Horiz.* 8: 1–6.
58. Ratner D and Ratner M (2003) *Nanotechnology and homeland security*. Prentice Hall PTR, Upper Saddle River.
59. The National Nanotechnology Initiative: Research and Development Leading to a Revolution in Technology and Industry, Supplement to the President’s FY 2007 Budget, http://www.nano.gov/NNI_07Budget.pdf
60. National Nanotechnology Initiative: Research and Development Leading to a Revolution in Technology and Industry Supplement to the President’s FY08 Budget, August 2007, http://nano.gov/NNI_08Budget.pdf
61. Department of Peace Studies of the University of Bradford (2008) *The biological and toxin weapons convention website*. <http://www.opbw.org/> Accessed 30 June 2008.
62. OPCW (2008) *Organisation for the prohibition of chemical weapons*. <http://www.opcw.org/> Accessed 30 June 2008.
63. The White House (2006) *The National Security Strategy*. <http://www.whitehouse.gov/nsc/nss/2006> Accessed 30 June 2008.
64. The White House (2002) *The National Security Strategy of the United States*. <http://www.whitehouse.gov/nsc/nss5.html> Accessed 30 June 2008.

65. The White House (2004) Biodefense for the 21st Century. <http://www.whitehouse.gov/homeland/20040430.html> Accessed 30 June 2008.
66. The White House (2002) National Strategy to Combat Weapons of Mass Destruction. <http://www.whitehouse.gov/news/releases/2002/12/WMDStrategy.pdf> Accessed 30 June 2008.
67. Joint Chiefs of Staff (2004) The National Military Strategy of the United States of America. <http://www.defenselink.mil/news/Mar2005/d20050318nms.pdf> Accessed 30 June 2008.
68. Joint Chiefs of Staff (2006) National Military Strategy to Combat Weapons of Mass Destruction. <http://www.defenselink.mil/pdf/NMS-CWMD2006.pdf> Accessed 30 June 2008.
69. Department of Defense (2006) Quadrennial Defense Review Report. <http://www.defenselink.mil/qdr/> Accessed 30 June 2008.
70. The National Strategy for Homeland Security (2002) <http://www.whitehouse.gov/homeland/book/> Accessed 30 June 2008.
71. Department of Homeland Security (2004) Securing our homeland. <http://www.dhs.gov/about/strategicplan> Accessed 30 June 2008.
72. Government Printing Office (2008) Budget of the United States Government. <http://origin.www.gpoaccess.gov/usbudget/> Accessed 30 June 2008.

Chapter 2

Implementing the Process

To address the potential for nanotechnology to impact chemical and biological (CB) defense and proliferation, the *Nanotechnology for Chemical and Biological Defense Project* – known as NanoCBD2030 – was designed to explore the potential use and misuse of nanoscience, nanotechnology, nanoengineering, and analogous emerging technologies in order to formulate a strategy to inform and guide the development of federal science and technology capabilities for the next 25 years.

The charges to those involved in all parts of this effort were the following:

1. Innovate solutions and strategize potential countermeasures to current CB threats leveraging revolutionary developments in nanotechnology,
2. Anticipate proliferation scenarios in which nanotechnology is put to malicious use by terrorists or nation-states,
3. Strategize potential countermeasures to defend against such uses, and
4. Recommend research directions and priorities to enable the long-term science capabilities for CB defense.

A significant part of the *Nanotechnology for Chemical and Biological Defense Project* was the workshop sponsored by the Department of Defense's Chemical and Biological Defense Program (CBDP), which brought together a diverse set of practitioners and researchers in Santa Fe, New Mexico in 2007. The workshop substantially contributed to the development of scenarios on and strategies regarding the potential benefits and threats of nanotechnology for national security.

This book attempts to capture the unique insights gleaned from a distinctive mix of leading experts in science, international security, military affairs, intelligence, medicine, engineering, and policy, who participated in various parts of this project, most notably as participants in the NanoCBD2030 Workshop. While logistical considerations limited the total number, the group comprised many individuals who have not been normally called on to evaluate this emerging intersection of science, technology, security, and policy. The study participants were selected to encourage the open exchange of intellectually provocative ideas and to entertain challenging concepts. The majority of the participants were chosen for their expertise with different aspects of CB defense or with nanotechnology – from the cutting edge scientific to operational, intelligence, economic, and political science experience. In addition to their

recognized expertise, participants were chosen on the basis of their diverse real-world operational and analytical experience.

An example of profound utility of having scientists and technologists interact more closely with operators can be found in the history of research on shipboard firefighting. A purely requirements-oriented approach drove researchers to develop bigger and more powerful nozzles to get more water to a fire faster and with higher velocity. In the 1980s, a technology was proposed that could pinpoint flame location through smoke and mist, which enabled the use of less but more precisely directed water to extinguish a fire. This realization drove basic science toward a new field of thermal imaging, rather than continuing only to improve fluid flow through nozzles.

The terms nanotechnology, nanoscience, and nanoengineering are broadly defined and applied in this book. Unless there is a specific reason for differentiating the terms, nanotechnology has been used throughout the study as a stand-in descriptor to encompass nanoscience, nanotechnology, and nanoengineering. In alignment with the National Nanotechnology Initiative definition, “nanotechnology is the ability to work – to see, measure, and manipulate – at the atomic, molecular, and supramolecular levels, in the length scale of approximately 1 to 100 nm range, with the goal of understanding and creating useful materials, devices, and systems that exploit the fundamentally new properties, phenomena, and functions resulting from their small structure.” Interaction distances are not the sole determinant of relevance; however, the emphasis is on the unique properties or capabilities that are conveyed at the nanoscale. Further, the term nanotechnology refers to more than working with a lone atom or single molecule. Working at the nanoscale may be most relevant when translated from the nanoscale through the micro- and mesoscale (“middle” scale) to the macroscale. As a result, the technologies and necessary infrastructure to interact, manipulate, and generate the materials or products on the nanoscience scale were also considered as part of the workshop. For example, a microelectronic mechanical system reactor capable of enabling self-assembled materials with unique properties at the nanoscale from macroscale fit well within the workshop and study charge.

Scenario-Based Planning

Scenario planning is a tool for ordering one's perceptions about alternative future environments in which one's decisions might be played out.

Peter Schwartz, 1996¹

A number of scenarios were considered that were based on combinations of various environmental factors. These were then used to generate recommendations for action, including a list of overarching, strategic research directions. The goal was to generate innovative and revolutionary concepts of the application of nanotechnology and analogous emerging technologies for CB defense and counterproliferation.

Scenarios are routinely used not only in corporate strategic planning² but also in public policy planning³ and national security planning.⁴ In finding ways to consider the key drivers and identify the more visionary paths, traditional “requirements-driven” planning for R&D is inadequate.⁵ A systematic method of long-term planning was needed that is more useful in cases of large uncertainties in the external drivers on the enterprise. Scenario-based planning endeavors to gain knowledge for the future by understanding the most uncertain and significant driving forces affecting potential outcomes. It is a group process which encourages learning and a better understanding of the nature and impact of organizational actions. The process is structured intentionally to break simple extrapolations and enable nonlinear and dynamic ways of capabilities-based planning. By setting discussions far enough in the future – far enough beyond facts and forecasts – discussants will encounter less defensive behavior and a more shared sense of purpose.⁶

The Process

The goal of this process was to identify major factors and events that would drive global change through 2030. To do this, four alternative global futures were developed in which these drivers would interact in different ways from the present through 25 years in the future. Each scenario was intended to lead to plausible, national security, and technology policy-relevant stories of how this future might evolve. Each story would highlight key uncertainties, discontinuities, and unlikely or “wild card” events, and identify important policy and technical challenges.

Technically robust scenarios may illustrate the potential malfeasant cooption of nanotechnology. Scenario analysis is useful for defense planning and resource allocation, with the goal to enable detection and possible interdiction before threats become imminent, to defeat nanotechnology-based threats at a distance, and to mitigate consequences of such an attack. Presenting scenarios in any area with risks for application to weapons must be approached with great sensitivity and consideration. In this process, scenarios were grounded thoroughly in observed scientific results available in the open literature. It was also important to exclude details an adversary would need to turn a concept into an operation or a technology into a weapon. The scenarios discussed herein are not intended to be exhaustive but are intended to help delineate the possible from the realm of science fantasy.

The subject matter of this chapter was approached with great sensitivity and care. Foremost, the scenarios described herein are grounded thoroughly in scientific research vetted through the open literature rather than in science fiction or fantasy. While all of the underlying science is real, the scenarios are notional. Operationalization of the threat scenarios or any individual threat was intentionally excluded. These scenarios are not a “terrorist roadmap” or even a guide for a well-financed state with advanced infrastructure. Additionally, scenarios that have previously been suggested, generally of the “nano-bot” or “grey goo” variety, are addressed and in some cases debunked. The degree of difficulty and intricacy of the scenarios varies

substantially. Steps 1–3 used in the overall study process were loosely based on Peter Schwartz’s scenario planning process.⁷

1. Independent drivers affecting the enterprise were identified and isolated for independent versus dependent variability. These factors included the relationship between science and national security, the unfolding science of nanotechnology, the underlying science of CB weapons, the perspective of the warfighter, and the pace of technology change.
2. From the independent drivers identified, two critical key drivers that are both important and the most uncertain were selected. The two key drivers that met this criterion were the pace of technology change – ranging from evolutionary to radical – and the evolving nature of warfare – ranging from traditional to highly irregular. This can be concisely portrayed in terms of the principal adversary to the US varying from a traditional Westphalian state to nonstate actors lacking a specific homeland. Plotting these two drivers orthogonally resulted in four speculative “worlds” that could exist in 2030, as shown in Fig. 2.1. The selection of these two drivers demonstrates the overarching relevance of the science and technology factors to defense policy and international security factors.
3. On the basis of the characteristics in each quadrant, notional scenarios – short stories – of potential futures were drafted.

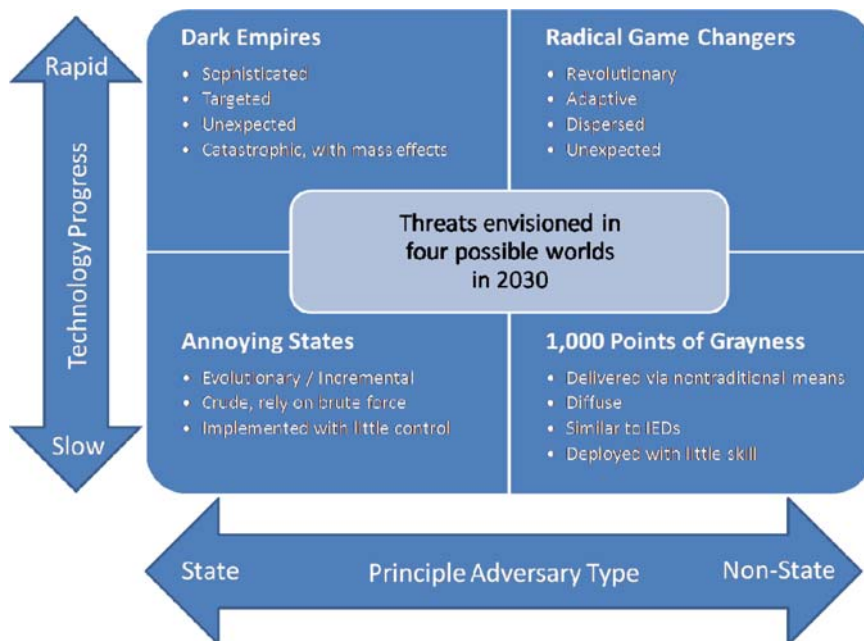


Fig. 2.1 The characteristic descriptors – shown in quadrants – of notional 2030 worlds that drove the scenario development process

4. After that, the implications of each scenario for the science and technology community were determined, including consideration of active “red-teaming” the defensive countermeasures and “blue-teaming” the proliferation scenarios. These implications are described in details in Chaps. 3 and 4.
5. On the basis of these implications, plausible research and development strategies to respond to each scenario’s implications were developed. These strategies are compiled in Chap. 5.
6. Finally, science and programmatic management policy recommendations to enable the US to respond more fully to current CB defense agents and future threats were developed. These recommendations are included in Chap. 5.

A more detailed discussion of the scenario process follows.

Creation of 2030 Worlds

Four worlds were envisioned, as shown in Fig. 2.1.

Radical Game Changers

Radical Game Changers is a 2030 world driven by nonstate actors and rapid technology development. It is a revolutionary, adaptive, and dispersed world, in which the unexpected routinely must be anticipated. The armed forces, civilian personnel, and national infrastructure are facing a new and radically different set of challenges. This world is characterized by asymmetric and nontraditional threats to the US. Sophisticated nonstate actors are likely to develop significant and unexpected set of CB agents that have the high potency and maximum detection and protection avoidance. Answering such radical challenges will require an equally radical change in the detection and protection strategies from known to unknown. In addition, the increased potency and lethality of these agents will drive diagnostic speed and increased integration between diagnostics and countermeasures. In addition to traditional investment to develop revolutionary capabilities, this world may likely require stronger interactions with nontraditional disciplines such as anthropology and more effective use of strategic communications.

Annoying States

Annoying States is a 2030 world driven by state actors and slow technology development. It is an evolutionary, traditional, incremental, and brute force world that extends linearly from traditional military operations – similar to many twentieth century low-level conflicts. In addition to concerns of proliferation of traditional twentieth century CB agents, improvised chemical or biological dispersive devices, such as those that co-opt industrial chemicals and basic industrial processes, are not atypical for this world. Drivers in this world include simple dispersion of classical

and industrial knowledge, increase in many small- or medium-sized regional state-on-state conflicts, the need for accurate monitoring, and the capability for quick attribution, as well as sharpened diplomacy.

Dark Empires

Dark Empires is a 2030 world of state actors and rapid technology development. It is a sophisticated world that deploys threats with catastrophic and mass effect and, in which, the unexpected routine must be anticipated. This class of scenarios deals with the technologically sophisticated state adversary capable of delivering multiple threats to multiple allied targets both domestic and overseas – the peer competitor, who will have not only a sizable uniformed military of its own but also intelligence and technological institutions on which to draw support. Innovation is highly likely, underpinned, and funded by large state institutions and access to materials, processes, and knowledge across a sophisticated technological state. Drivers include prevention through international diplomatic means (both traditional and new), large-scale, integrated monitoring capabilities, as well as quick and robust attribution and response.

1,000 Points of Grayness

1,000 Points of Grayness is a 2030 world driven by nonstate actors and slow technology development. This is a diffuse world which subverts traditional delivery systems or benevolent commercial technology and turns them into threatening and indiscriminate purposes, using relatively unskilled technologies to pursue disperse insurgent tactics. Like the Annoying States world, crude improvised chemical or biological dispersive devices, such as those that co-opt industrial chemicals, are not atypical for this world. Like the Radical Game Changers World, this world will likely require stronger interactions with nontraditional disciplines, such as anthropology, human terrain knowledge, and more effective use of strategic communications.

Envisioning Scenarios in the Four Worlds

In order to encourage disruptive leaps forward in nanotechnologies and enabling systems and minimize linear extrapolation, the setting for construction of the notional scenarios was such that one might imagine falling asleep and awakening in 2030 in each of these four possible worlds. The “four worlds” (or quadrants) have different assumptions about the pace of technology change over the next 20 years and include consideration of accessibility, cost, globalization, economic, social, and political factors. These are matrixed against a consideration of traditional “state-based” enemies and the more irregular “nonstate” adversaries. Within the workshop setting, participants were divided into focus groups for the development of specific scenarios. The groups were charged to examine the

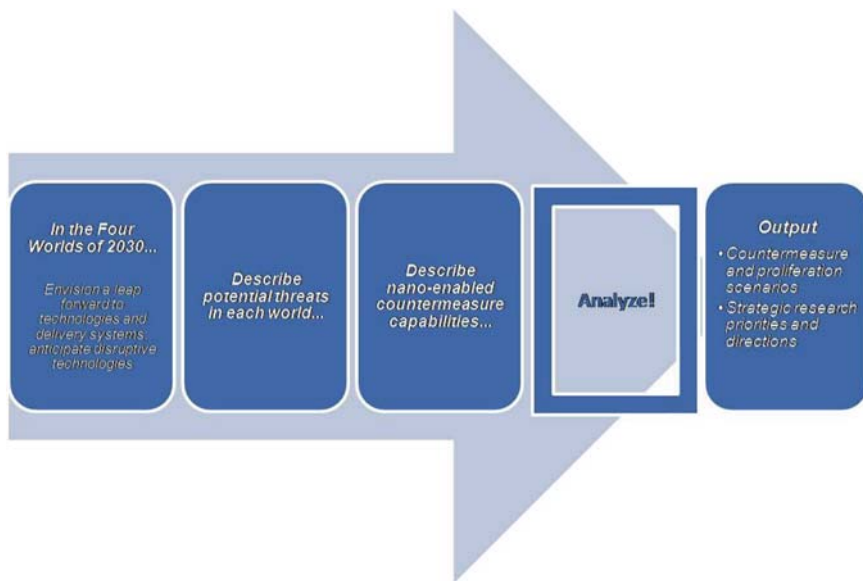


Fig. 2.2 Overall process

development of countermeasures and the challenges of malfeasant cooption of nanotechnology. This process is shown in Fig. 2.2.

For countermeasures development, possible CB defense capabilities against areas where the US currently lacks solutions or has less than ideal passive defense capabilities were explored. One example is standoff biological detection or feather-weight personal protection filters. Ideas were separated in to four general areas: (1a) detection and diagnostics of biological agents, (1b) detection and diagnostics of chemical agents, (2) physical protection, (3) decontamination, remediation, and consequence management, and (4) medical countermeasures. Each area had some overlap, which became more apparent throughout the course of the project.

For each quadrant of the worlds, the desired state of countermeasure development was conceived and then new fields that could contribute to capability development were identified. Additionally, enabling infrastructures upon which such capabilities will depend and the limits to the use of countermeasure against different adversary types were considered.

For the misuse of nanotechnology, the groups explored scenarios in which state or nonstate adversaries might use nanotechnology applications against the US and allies. These groups also considered proliferation challenges. The specific threats considered were new or nanoenabled biochemical agents; malfeasant exploitation of the toxicological or other deleterious health effects; evasion of vaccines, innate human immunity, or other medical countermeasures; and self-assembled materials and devices to molecular assemblers. All of the scenarios developed were based on sound scientific principles and within technical capability of the best scientists in the best laboratories; they also purposely lack meaningful concepts of battlefield operations.

For each quadrant of the worlds, the focus groups then asked how nanotechnology might be used against US forces and our allies. They looked at the worst, technically reasonable scenarios. Other questions also included the consequences of the principal threats, and whether they are catastrophic or of limited use. This included discussion of how weapons might be delivered and the enabling infrastructure required. The limits to acquisition by the different adversary types were also discussed, and finally, the factors that could drive proliferation forward or hinder it.

After presenting the scenarios to the overall workshop, the focus groups shifted emphasis to identifying and developing research directions with strong science and national security justification to achieve those 2030 capabilities for countermeasures and strategies toward limiting the threat of malevolent actors, realizing any part of the 2030 proliferation scenarios. General considerations included the identification of supporting research directions needed and bottlenecks to overcome to achieve success, delineation of factors – technical and nontechnical – that would slow or speed development of countermeasure capabilities or threats, and articulation of key developments (breakthroughs, new platforms, and enabling infrastructure, and so on) that have to occur by 2010 and 2020 for the 2030 scenarios to occur.

For the challenges of malevolent cooption of nanotechnology, the participants also identified critical nodes or events to interdict negative consequences or crucial development points that are most disconcerting from a national security perspective, that is, places where effective programs can be implemented to prevent or limit a threat. Participants also considered the overall national security component supporting the need to develop such capabilities or the need to decrease the risk of a proliferation scenario. As a final component, the workshop considered the types of organizations or research entities that might be fostered in order to generate the innovative and revolutionary countermeasures for 2030.

Using Scenarios to Roadmap and Prioritize

The scenarios generated in this process were used to help guide different communities – scientists, technologists, manufacturers, and end-users – to narrow their focus on technology drivers and to generate relevant research needs. At the end of the process, the scenarios were ranked by the attendees at the workshop using a balloting method to help pinpoint the highest priorities. This method took all viewpoints into account and resulted in a high fidelity list. These results are described further in Chapters 3 and 4 and the details are listed in Chapter 6.

Value of This Approach

The NanoCBD2030 workshop and study gives the national and homeland security science and technology communities a forward-leaning roadmap of research

directions for nanotechnology applications in CB defense. The process provides the DoD with an effective means of planning research and development tactics for relevant nanotechnology applications. The resulting recommendations can be leveraged for homeland security as well as such complementary aspects as intelligence and diplomacy, adding additional value to the effort. The strategic directions generated by the NanoCBD2030 Project have been used in the DoD's planning and budget process, and these outcomes will continue to influence the development of future directions for the nation.

References

1. Schwartz P (1996) *The art of the long view: Planning for the future in an uncertain world*. Doubleday Business, New York.
2. Wack P (1985) The gentle art of re-perceiving, *Harvard Business Review*. September-October: 73–89.
3. Kahn H (1960) *On Thermonuclear War*. Greenwood Press, West Port.
4. National Intelligence Council (2000) *Global Trends 2015: A Dialogue About the Future with Nongovernment Experts*. Government Printing Office 041-015-00211-2. http://www.dni.gov/nic/PDF_GIF_global/globaltrend2015.pdf Accessed 30 June 2008.
5. Department of Defense (2006) *Defense Science Board Summer Study on 21st Century Technology Vectors*. <http://www.acq.osd.mil/dsb/reports.htm> Accessed 30 June 2008.
6. Ringland G (2002) *Scenario Planning Managing for the Future*. Wiley, Chichester.
7. Schwartz P (1996) *The art of the long view: planning for the future in an uncertain world*. Doubleday Business, New York.

Chapter 3

Applying Nanotechnology to Revolutionary Chemical and Biological Countermeasures

Basic research in nanoscience, funded by governments and industries around the world, has grown dramatically in the last decade. Nanotechnology is expected to affect the world in important ways, much as the chemical, semiconductor, and biotechnology industries have done over the past 75 years. There is tremendous interest and commensurate investment in the potential for scientific discovery at the nanoscale to deliver revolutionary breakthroughs in medicine, computing, materials, and consumer goods. As researchers continue to explore and understand the unique physical phenomena of engineered nanomaterials, technologies employing novel nanoscience will begin to impact all technologies, including chemical and biological (CB) defense applications.

This chapter will examine nanotechnology's possible applications in CB defense in four technical areas: physical protection, detection and diagnostics, decontamination, and medical countermeasures. Each section will open with scenarios that were developed and their implications and an overview of the technology area. This is followed by a discussion of the implications of nanotechnology progress with regard to each of the critical technology areas, and will conclude with a listing of possible solutions needed in 2010, 2020, and 2030.

Progress at the Nanoscale

Among the many envisioned applications of nanotechnology of substantial interest for defensive weapons and military aspects are sensor systems. For example, semiconducting nanocrystals – often called quantum dots or nanodots – have the potential to detect single molecules of a target substance. These are essentially very small transistors that produce a unique optical signal that can be changed by the addition or removal of an electron. Detectors using quantum dots could better detect solids and liquids with low vapor pressure, such as high explosives and some classes of nerve agents. Nanostructured materials have already been investigated for standoff detection of CB agents and explosive vapor detection.¹ Nanodots have also been designed for detection of specific biological moieties,^{2–5} which may lead

to detection methodologies for infectious diseases or anthrax spores, potentially displacing today's state-of-the art immunoassay and PCR-based DNA detectors. All this demonstrates the undeniable potential and benefits of nanoscale science. The application of emerging nanotechnologies will affect all aspects of CB countermeasures, from improving physical protection, refining the sensitivity and selectivity of sensors, to advancing decontamination and medical treatments.

The current state of knowledge of nanomaterials can be compared with the synthetic chemicals 75 years ago: a host of discoveries and interesting materials – nylon, Teflon, nitrogen compounds, aromatics, pure alkanes, and so on – were being uncovered, but very little fundamental predictability in molecular synthesis was possible. Now, 75 years later, chemists can imagine almost any molecule and then synthesize it in one of the most intellectually challenging pursuits and accomplishments of the human mind. Synthetic chemistry can be likened to a giant three-dimensional puzzle coupled with a game of chess that continually yields riches for civilization. Nanotechnology undoubtedly holds similar promise.

In the fight against CB threats, the battleground can be delineated in four areas. The first is physical protection for people and equipment. The second is detection and diagnostics of the threat location and nature. The goal of both of these is to evade the threat. If the threat cannot be avoided, the third battle is decontamination of equipment and infrastructure, and fourth is medical countermeasures for affected personnel. The potential for nanotechnology to aid these four thrusts is described in detail here.

Physical Protection

The 2008 Department of Defense Chemical and Biological Defense Program Annual Report to Congress defines protection as providing life sustainment and continued operational capability in a CBRN (chemical, biological, radiological, or nuclear) contaminated environment.⁶ A complete battlefield protection program addresses both individual and collective protection to the warfighter from inhalation, ingestion, or contact with dangerous agent, and the capability to shield small groups of warfighters and their support teams.

Efforts in this area include protective clothing, protective masks, air purification, and shelters. The effective level of protection and the capabilities of the fielded equipment will increasingly depend on the transition of new materials and processing concepts to manufacturing. Successful utilization of nanoscale materials technology is expected to result in a significant improvement in warfighter protection over that provided today. A number of scenarios in the four worlds of 2030 are shown in Fig. 3.1.

Individual protection must provide protection from an ever-changing threat scenario, while maximizing the effectiveness of the individual warfighter. Chemical and biological threats are physically transmitted to the warfighter as aerosols, vapors, and liquids, or through direct contact with such contaminated materials as

Dark Empires In a standoff against a peer competitor in the world of <u>Dark Empires</u>, missiles are launched against a Cruiser patrolling in international waters. Ballistic intercept destroys the first wave of traditional missiles; the debris, however, disseminates a previously unknown chemical agent. Collective protection installed on the ship is equipped with reactive nanoporous intelligent material as part of a test system. The intelligent materials are able to respond to the unknown material and initiate protective response across the entire ship.	Radical Game Changers While executing counterinsurgency operations, a military unit is intentionally contaminated with nanoengineered biological agent invisible to traditional detection systems. In the world of <u>Radical Game Changers</u>, the soldiers are equipped with "Borg Shield" technology that quickly recognizes the exposure, protecting them by encapsulating the agent and alerting them to don their masks or other supplemental personal protective measures.
Annoying States During military support of transition and reconstruction operations, aerosolizing devices hidden in plain carrier bags simultaneously release an unknown chemical agent at the perimeters of several Forward Operating Sites (FOS). Undetectable to the human eye, the troops respond to a visual warning from their military-issue sunglasses. The glasses are coated with a nanoscale film that analyzes the threat and informs them that their protective "sunblock"—which contains reactive adsorptive nanoparticles—will protect them. Nanoparticles are also able identify the spatial extent of the contamination. When such nanoparticles come in contact with a chemical or biological agent, the nanoparticles signal (e.g., with light) the presence, concentration, and type of CB agent. During decontamination, the efficacy of decontamination can be measured. After the full decontamination, each soldier applies a lotion to detect any remaining trace of the chemical agent. In the world of <u>Annoying States</u>, this is a typical attack: it is well-coordinated using known technology.	1,000 Points of Grayness An IED detonates near a Special Forces team conducting training of indigenous forces on special operations as part of a stability mission. A few minutes later, a secondary device is triggered that bubbles a stream of a toxic industrial chemical (TIC) onto the ground under the injured team members. The next-generation Army Combat Uniforms (ACUs) detect the TIC and transmit a signal to the team's commander. Nanoabsorbents in the uniform's fabric selectively encapsulate and neutralize the TIC—all transparent to the soldiers. The Communications Sergeant is automatically updated on the status for each team member's ACU to ensure readiness. In the world of <u>1000 Points of Grayness</u>, this is a co-option of a commercially-available technology for hostile purposes perpetrated by an unpredictable foe.

Fig. 3.1 Selected physical protection scenarios

soil, water, food, and surfaces. The current strategy to respond to these threats on the battlefield is a doctrine of mission-oriented protective posture (MOPP) levels, a protocol to determine the necessary level of coverage required to protect the warfighter from mission-specific threats. A battlefield commander determines the MOPP level based on the best available intelligence. MOPP levels range from 0 to 4 and are depicted in Fig. 3.2.⁷

- MOPP Level 0 – protective equipment is readily available, but is not worn
- MOPP Level 1 – overgarment and helmet cover are worn; CB attacks are possible
- MOPP Level 2 – overboots are added; CB attacks are probable
- MOPP Level 3 – chemical mask and hood are added; used after chemicals have been employed by the enemy, but in areas with negligible hazard
- MOPP Level 4 – butyl rubber gloves are added

The joint service lightweight integrated suit technology (JSLIST) over-garment currently provides the protective clothing solution for MOPP.⁸ This nylon and cotton garment is worn over a duty uniform or undergarments and can weigh up to 7 lb.



Fig. 3.2 Coverage at different MOPP levels. *Note:* The soldiers in the pictures are not wearing head coverings. While performing military operations all personnel wear helmets. At MOPP levels other than MOPP-0 personnel may also wear chemical protective helmet cover. *Source:* Information paper available at <http://gulflink.osd.mil/mopp/index.html>

It is compatible with protective gloves, footwear, and mask. This ensemble combination provides effective CB protection against percutaneous and respiratory exposure to all known CB threat agents. The JSLIST protects by adsorbing toxic agents onto high-surface-area carbon spheres.

The JSLIST garment can be worn for up to 45 days with six launderings, and is designed to provide 24 h of protection against battlefield concentrations of agent. The JSLIST is more durable, lighter weight, has enhanced suit closures for a better fit, and results in a 15% reduction in heat stress for the wearer as compared with previous protective garments. Each JSLIST component is based on state-of-the-art material technologies that have undergone extensive user evaluation and field and laboratory testing.

Even with these improvements, the field commander faces the dilemma of reducing warfighter effectiveness with each increase in MOPP Level. Wearing the protective gear results in heat stress, reduced visibility, fatigue, and cognitive stress.⁹ These factors, coupled with battlefield stress, can cause dramatic decreases in situational awareness and cognitive performance. The commander must weigh the potential of a CBRN attack against this reduction in combat effectiveness. If it is assumed that the battlefield of the future will pose an even greater use of CB threats, then a better system of protection is required.

Implications of Advances via Nanotechnology

The emerging technical advances in nanotechnology may provide opportunities to provide physical protection and enhance performance of warfighters. Current research is aimed at advanced materials and coatings that will provide protection from both ballistic threats and CB threats. The goal is a standard uniform capable

of automatically responding to threat changes without increasing warfighter decision-making or logistical burdens. The material solutions developed for such uniforms would also be applicable to other equipment such as tents and vehicles.

Future uniforms require self-awareness and the capability to respond nearly instantaneously to conditions. For example, a protective system could “harden” as necessary to prevent ballistic penetration or limit radiological exposure. A protective system may also need to be “hardened” against electromagnetic disruption of embedded electrical micro- or nanoscale systems. The ideal system should also monitor the physiological condition of the soldier, ensure thermal homeostasis, as well as protect from insects and pests. A semipermeable membrane could neutralize chemical or biological threats before they reach the warfighter. A key aspect of such an ensemble could be a network of sensors acting in unison to sense ambient threats, to report incoming threats to the individual, and to broadcast this knowledge to other protective systems in the area. An advanced uniform system could react autonomously to ambient threats as well as warnings broadcast from other systems, without conscious decisions by the deployed warfighter.

Leading the current effort in advancing nanoscience application to soldier safety is the US Army Natick Soldier Research, Development and Engineering Center with programs including the Institute for Soldier Nanotechnologies. This program and a number of emerging efforts from other government laboratories, universities, and industry are investigating the application of nanotechnologies to develop new materials to respond to battlefield threats and to monitor and respond to the warfighter’s health. The combined effort of all of these current research programs, and those yet to start, will be needed to deliver this needed warfighter protective system.

Possible Solutions in 2030

The broad spectrum of battlefield threats projected in the four 2030 worlds described in Chap. 2 will require differing physical protection strategies. The threats projected for the worlds of *Annoying States* and *1,000 Points of Grayness* represent the lowest level of technological advancement and organization. Just as today, these worlds will likely involve numerous events that are lethal and small in scale. The majority of the battlefield threats in these worlds are expected to stem more often from conventional explosives and improvised explosive devices than from chemical or biological weapons. As they are today, explosives may remain the tactical weapon of choice owing to their ease of use and proven lethality. Nonetheless, crude improvised chemical or biological dispersive devices, such as those that co-opt toxic industrial chemicals, are not atypical for the worlds of *Annoying States* and *1,000 Points of Grayness*. The potential strategic value of CB threats as weapons of terror and disruption keeps their threat high, and increases the burden on responders in urban conflicts involving terrorism or insurgency targeting the civilian population. Without advanced systems, a toxic cloud released during a military conflict or in a civilian environment is likely to negatively impact all parties.

The world of *Dark Empires* is a truly threatening conflict environment characterized by sophisticated and highly lethal CB agents and weapons systems emerging from states possessing a high degree of organization and supported by a robust technological and economic base. Such states may also have an active espionage establishment. Adversaries in the world of *Dark Empires* are likely to have the most technically sophisticated – although not the only and not necessarily the most effective – means to overcome defensive countermeasures. Such a world does not have the randomness and utter unpredictability evident in the worlds *1,000 Points of Grayness* and *Radical Game Changers*. The *Dark Empires* are, however, the most likely origin of large-scale disruptive weapons systems.

The world of *Radical Game Changers* poses threat and uncertainty in equal measures affecting planning and preparation. While lacking the institutions and apparatuses of a state, the *Radical Game Changers* exist in a world of (1) large-scale technology dispersion providing access to advanced methods for dispersing goals, tactics, and strategies quickly; (2) access to advanced materials, techniques, and knowledge; and (3) increased transnational activity, both legitimate and criminal. *Radical Game Changers* may have tacit or covert support by a state but they do not have the same standing in the international community nor do they have a specific homeland that could be targeted for retribution.

System Design Considerations

While it is difficult to predict the specific nature of the future suite of CB threats that will become available, all threats will most likely share three basic transport mechanisms – inhalation, ingestion, and percutaneous absorption of threat agent. Consequently, in all scenarios, the need exists to provide physical protection from all three. Protection at this scale can be accomplished, in the future as today, by covering the entire body and providing adsorbent and particulate air filtration. Unlike current strategy, however, a future warrior uniform would not require the warrior to don additional layers for protection from CB threats, but it would rather provide that capability as an integral and transparent part of the standard uniform.

The 2030 protective uniform may more closely resemble a system of interacting active sensors and stimulus responding intelligent materials than the passive material of today's JSLIST. The future of personal protection, enabled by bionanotechnology and nano-engineered materials, identifies, instantly responds, and communicates information about threats from blast, small arms, radiological, and chemical and biological sources. Such a protective system should neutralize threats near or at the surface of the uniform before they can come into direct physical contact with the warrior. Active material properties – ion channels and functionalized nanolayers, for example – are two approaches being investigated today at the basic research level to accomplish this.¹⁰ In addition to foreseeing such active approaches integrated into personal protection, the individual reactive entities should communicate near-instantaneously, whether chemically, magnetically, or electrically, with other entities on the suit and communication initial assessment of threat to external systems. This future of personal protection envisions a network-aware system that would be capable of

sharing data from its own integrated sensor system with the surrounding network, and in doing so, the system would become a true intelligent system of systems.

Potential attributes include the capability to block incoming threats while managing body moisture and heat to maintain comfort. New materials could accomplish these tasks on the nanoscale by using electric and magnetic fields, as well as other mechanisms, to adjust the hydrophobicity and hydrophilicity of surfaces.¹¹ Material surfaces may also induce nanoparticle agglomeration and clustering to promote threat sequestration and neutralization. Multifunctional nanofiber structures incorporating high-capacity selective adsorbents, such as metal organic frameworks (MOF)¹² or metal organic polyhedras,¹³ are one route to enabling capabilities to neutralize or to safely sequester hazardous breakdown products in nanoscale traps (see Fig. 3.3).

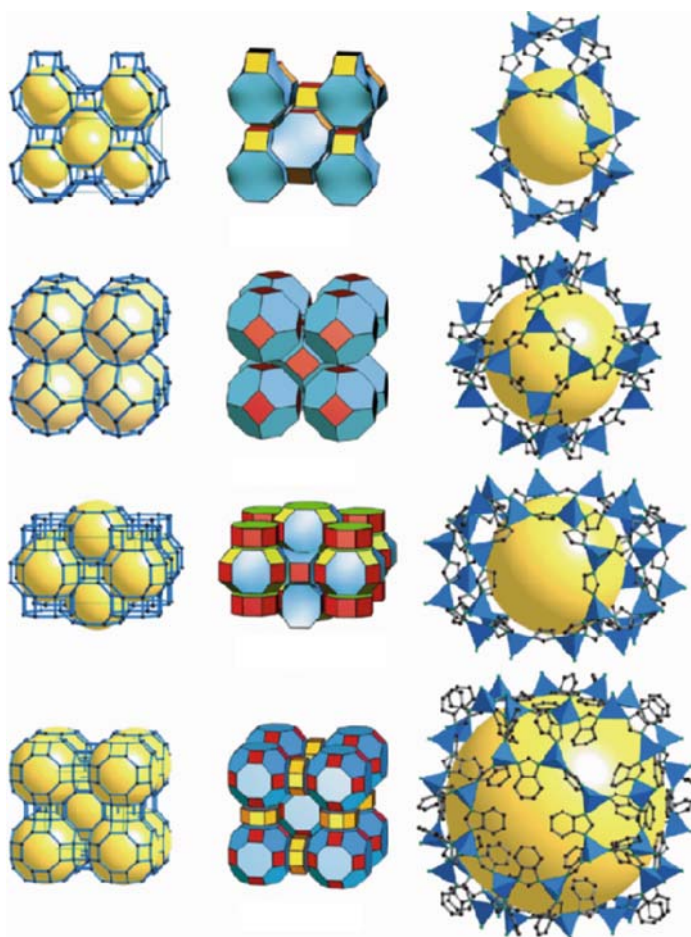


Fig. 3.3 The single crystal X-ray structures of zeolitic imidazolate metal-oxide frameworks (MOFs). In each row, the net is shown as a stick diagram (*left*) and as a tiling (*center*). The largest cage in each MOF is shown with ZnN_4 tetrahedra in blue (*right*). H atoms are omitted for clarity¹⁶¹

To be effective, such new materials must be durable and robust enough to withstand exposure to common chemicals found in fuels, oils, insecticides, cleaners, flavored coffee, and highly caffeinated and carbonated energy drinks; salt spray; dust; and changes in heat and humidity – through months of harsh use. In addition, many of these desired capabilities will require power to operate, so the suit may also harvest energy from available sources, such as a combination of body heat and motion or solar energy.

Establishing the manufacturing tech base that is capable of producing the required advanced materials, fabrics, sensors, and systems integration is a key component to successful realization of such revolutionary capability and fielding the envisioned future warrior uniform. It is also one that is many times not addressed in strategies emphasizing basic research or applied technology development. To successfully develop this system, the industrial backbone to produce these ideal materials, their secondary, tertiary, and quaternary structural components, and their interface with the information system or sensor network, would also be established by 2030. Furthermore, this technology base infrastructure must respond quickly to the changing threat scenarios of the future through an established capability to produce materials that are designed from basic scientific principles. Today's methods are inefficient and commonly based on trial and error, which are not capable of producing new materials in a consistent, uniform manner. This technology base must be capable of rapidly moving from the analysis of a threat, through the atomic level design of appropriate materials to counter the threat, into the production of the appropriate fabrics and coatings in a nearly seamless manner.

In assessing the transfer of a technology from the laboratory to a manufacturing base, the critical and complicated nature of the current process can be appreciated using the manufacturing readiness levels (MRL). While a technology is still to be developed and before a technology is transitioned to engineering and development, the program manager within DoD can request a determination of MRL for those capabilities (technologies) showing promise for further development.

It is possible that a technology may have a very high technology readiness level but still have a low MRL – and the state of the manufacturing tech base then limits the potential to transition the technology. A potentially more useful standard may be the integration readiness level, a measure of the ability to integrate individual components of a complex system, i.e., an intelligent suit that may incorporate sensors, biological membranes, and power systems. In this case, each technology may be mature, and manufacturable in quantity, but the level of the integrated whole is lower than the individual systems.

This illustrates the holistic nature of transitioning technologies through advanced development and engineering to the manufacturing tech base. The program manager's involvement in monitoring the tech base can facilitate movement of technology to the field, perhaps by supporting early studies to determine manufacturing and integration readiness levels. The development of flexible mechanisms for positive change can also facilitate the implementation of results of such studies.

Further, particularly in *Dark Empire* type scenarios, preventing adversaries from benefiting from new technologies must be considered. This is complicated in the increasingly globalized nature of innovation, development, and the market that

characterizes technologically driven business. One approach has been through the trusted access program and certification of trusted foundries for acquisition of integrated circuits for the DoD and the intelligence community. Through the trusted access program, a mechanism to guarantee access to trusted microelectronics technologies for critical defense and security system needs now and into the future has been created.¹⁴ The program was initiated in response to concerns about the security of offshore manufacturing facilities.¹⁵ Historically, the National Security Agency had manufactured secure microelectronics needed for sensitive applications across the US Government. As the pace of semiconductor innovation and commercial development – including foreign-based advancements – accelerated, a new and more efficient mechanism was needed. Similarly, successful production of new nanoenabled materials will require a combination of effective communication of technology gaps along with long-term support necessary to attract quality researchers and risk takers that will expand the commercial nanotechnology product development base.

Operational Considerations

The intent of the physical protection suit of 2030 – an effective *Borg Shield* – is to provide protection from all CB threats encountered in the environment, including toxic industrial chemicals, toxic industrial materials, and novel or newly engineered biological or chemical agents. The *Borg Shield* will successfully protect the warfighter from such threats by interdicting agent before contact with the body (see Fig. 3.4). Preventing the introduction of a pathway that allows direct contact with the body is important. The overall goal is a situation where CB threats are routinely and transparently neutralized – and therefore less likely to be deployed by adversaries.



Fig. 3.4 Hollywood warfighter suit of the future: The Borg from Star Trek, showing the Borg Shield repelling phaser fire. Tagline: “Sir, they’ve adapted”

Red-teaming analyses highlight several approaches to violating the protective seal provided by the 2030 uniform. For example, today's warfighters have discovered that fine sand can get through even the best seals, and nanoscale particles can only be more invasive. A future suit would need the ability to seal itself from nanoscale threats without compromising other characteristics.

Degradation of the suit may also be effected by corrosive substances; delivery of such substances on a large scale may compromise a suit designed to ward off vapors. Physical and mechanical penetration of the suit may require additional protection. To achieve this, the suit may be designed to prevent penetration by ballistic or other impacts as a normal requirement. For example, the negative impact of normal cutting and scratching of the fabric can be minimized by using nanolayered, self-healing materials. An optimized shield could provide adequate protection from CB threats, as well as provide protection from more common ballistic threats.

Pathways to Achieve Physical Protection

Producing an ensemble with the properties of a "Borg Shield" by 2030 will require transitioning the appropriate basic research efforts out of the laboratory to an expanding manufacturing base. At a minimum, the goal of physical protection is to produce intelligent materials that can detect and block all threats – aerosols, vapors, and liquids – while improving the safety and comfort of the warfighter. This involves identifying, evaluating, and promoting technologies that are currently in development, as well as creating the academic and commercial critical mass required to move to the next generation of material development and production. A list of desired capabilities is provided in Table 3.1. To accomplish this, a science-based, multidisciplinary process is needed that is closely coupled to the manufacturing technology base.

To date, efforts that could contribute to 2030 capability needs have primarily focused separately on the development of sensors, on the development of the materials, or on development of integrated networked systems. In an effective development program, all are driven from the beginning with knowledge and interaction with the other. This does not mean a single project or program in which every piece is lock-step across interdisciplinary divides. To realize revolutionary capabilities, knowledge must be deep and substantial within each of the individual disciplines. At the core is a fundamental understanding of how threat agents are neutralized. Without this, development of nanomaterials for agent neutralization is trial and error. It may result in a solution but will not do so efficiently, and it is unlikely to be the best solution. To gain this intrinsic understanding for neutralization of CB agents, computational chemistry and systems biology modeling, along with experiments exploring the hydrolytic and oxidative mechanisms and reactions for CB agent decontamination, are needed. Research path priorities identified by this basic research could then be pursued to develop advanced agent decontamination technologies.

Applying a similar informatics approach to material properties depends first on an atomic and molecular level understanding of potential materials. If

Table 3.1 Capabilities desired for the development of the 2030 personal protective ensemble

Shielding system for individuals, equipment, and supplies
• Individual uniforms can work autonomously by responding to trigger stimuli • Uniforms can communicate and collectively respond to protect groups of individuals • Systems include protection from blast, ballistic, and CB threats
Multiuse materials
• Effective materials to protect buildings, tents, vehicles, and warfighters • Sensors systems with high confidence and low uncertainty response, that provide dynamic updating of threat conditions coordinated with real-time material response • Smart fabrics that communicate threats with surrounding systems • Failsafe coatings and fiber-based sensors that indicate contamination through color changes or other means
Large-scale manufacturing
• Industrial supply chain capable of rapidly designing and producing materials to counter emerging threats • Nanomanufacturing capacity for the building blocks – nanoparticles, nanofibers, and nano-scale coatings
Library of materials and properties for nanomaterials
• Atomic and molecular level understanding of nanoscale structure, properties, and chemical interactions • Available high-performance computing capability to support first principle modeling and simulation • Verification and validation of components and systems • Available libraries of materials and design properties

implemented, this could result in a new paradigm of rational design of materials through an understanding of structure, properties, and chemical interactions. Expanding this method to include compounds with diverse structures, compositions, and properties could aid in the development of materials with hybrid or tailored properties.

Analyzing and optimizing the results of these types of investigations will require an investment in supercomputing capabilities to develop and test models and simulations. Leveraging across the federal government should be pursued in this area. Verification and validation of these specialized models and simulations is a critical step and would require additional key experiments, as well as availability of facilities and trained personal to work safely with live agents, both biological and chemical.

Design Challenges for 2010

Requirements development includes both the identification of perceived needs and measurements of real needs. For example, the suit's mask must allow the operator to maintain situational awareness of both surroundings and the protective system status. Development of these systems must be performed in close consultation with the operator community, who provide critical data on human factors as well as appropriate validation and testing procedures. Performance characteristics and threat specifications will require research to optimize the operation and protection factors. This will likely require

the establishment of new testing methodologies, capabilities, and facilities. If the approach is successful, the testing capabilities may need to accommodate high throughput and the flexibility to adjust to future novel approaches.

Materials informatics – properties libraries, models, and simulations¹⁶ – for protective materials will evolve over time. One of the most important tasks in the near term is building the infrastructure for developing, maintaining, and adding new library capacity. A first step is acquiring data to define the design of the primary structure of relevant materials. Actual design of materials based upon data in these libraries will not be possible at first as the data are not complete nor will the necessary models and simulations be functional.

A second near term focus to meet the 2030 goals must push laboratory research out to the commercial world. This will encourage incremental improvements to existing protective gear and can provide incentives for investment by the private sector to establish nanomanufacturing capabilities. Early stage mass manufacturing of such embedded technologies as quantum tunneling sensors and nanofiber arrays is also needed by 2010.

The capacity to manufacture self-decontaminating and self-detoxifying materials is likely available in the near term. Smart materials may also be emerging from the industrial base for widespread implementation into commercial products. These materials are able to change porosity and surface energy on demand.¹⁷ Electric or magnetic fields, for example, may be applied to adjust the diameter of pores in a material from 0.5 nm to 10 μm .¹⁸ A parallel area of research that may drive large-scale realization of such nano-engineered materials is fuel cell research and development.¹⁹ New materials for fuel cell membranes^{20,21} are likely to enable smaller systems that work with energy harvesting schemes. A critical factor is the alignment of technology development to incorporate these novel materials into existing platforms using scalable manufacturing processes.

Self-cleaning materials are an additional area of basic nanoscience research currently under exploration for direct use in protection, as well as other nontraditional applications such as commercial building materials.²² One route has been to design synthetic mimics of micro- and nanotextured surfaces of hydrophobic plant leaves.²³ Another biomimetic approach to replicate hydrophobic surfaces characterized by a combination of surface coating and roughness determines the level of water repellence and thus the self-cleaning capacity of the material.²⁴ Future capabilities are suggested by the ability to tailor self-assembling surface materials with specific responses, such as de-wetting.²⁵ Additional experimental work to enable further a priori design and allow functional control of self-cleaning materials by a user is needed, as well as integration into an overall ensemble. See Fig. 3.5 for an example from nature.

Design Challenges for 2020

By the mid-point on the way to 2030, investment is expected to result in significant advancement in enabling technologies and the manufacturing base. These advancements may include an ensemble of embeddable sensor technologies with tailored selectivity and specificity and a high level of certainty. Such sensors will be

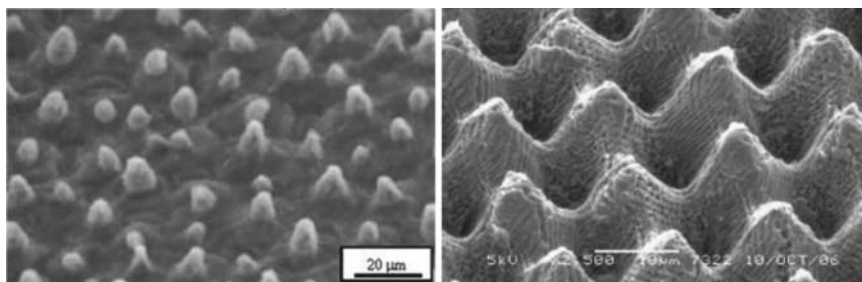


Fig. 3.5 (Left) Scanning electron micrograph image of the surface of a lotus leaf. Ohio State University engineers are using the bumpy leaf as a model for slick, water-repellent surfaces. The species of lotus shown here is *Nelumbia nucifera*. Image courtesy of Prof. Bharat Bhushan, Ohio Eminent Scholar and The Howard D. Winbigler Professor, Director, Nanoprobe Laboratory for Bio- and Nanotechnology and Biomimetics (NLB2), Ohio State University. (Right) The double nanoscale structure (pillars with ripples on them) is clearly visible in this polymeric surface. Image courtesy of Ir. Max Groenendijk, Lightmotif B.V., Campus University of Twente, Building Horst

amenable to ruggedized equipment, able to rapidly detect minimal concentrations in difficult environments. New materials for power systems, perhaps enabling hydrogen storage at ambient temperatures, may also be available.

The libraries of properties at this juncture may be populated with the significant materials and hybrid structures, including their secondary and tertiary structures and specificity. By 2020, the basic scientific understanding of these structures will provide the beginning of a deterministic control of function and performance of materials to allow for the successful design of new materials for desired capabilities. The library will also include hybrid properties for multifunctional materials and composites. As it becomes available, this primary data will provide the knowledge base to move the manufacturing technology base to the goal of producing materials directly from sophisticated models.

By 2020, a viable industrial infrastructure needs to emerge that is capable of producing significant quantities of materials with predetermined properties, albeit with limited functionality. New, or appropriately modified, industrial standards should be in place at this point for nanomanufactured materials. These standards are needed to evaluate the quality and reliability of the materials as well as to prove the safety and reliability required for mass acceptance.

To facilitate a full systems approach to designing physical protection from CB threats by 2020 will require coordination with academic curricula and research programs. Effective integration of sensor data with material response will need directed research and development, as will verification and validation programs of these systems. Appropriate infrastructure – testing facilities and equipment, and enhanced supercomputing facilities – may be focused on this problem domain at DoD and Department of Energy laboratories.

The final phase toward meeting the 2030 physical protection objectives is the initiation of a 5-year program in 2025 to prototype an integrated nanoenabled system.

Table 3.2 Essential components for advancement to desired 2030 state for physical protection

By 2010	By 2020	By 2030
Protection structure • Focus on design of primary structure and engineering the backbone • Ability to fabricate and control any atomic structure	Protection system • Deterministic control of functions and performance, including ability to neutralize, heal, or shed threats Embedded sensors	Integration • Integrate new materials with secondary and tertiary structures, with quaternary sensor structure to make very smart, very robust material • Individual shields function autonomously (e.g., respond to a trigger) to detect, diagnose, and decontaminate
Embedded sensors • Piezoelectric materials • Quantum tunneling • Nanofiber arrays	• Enhanced selectivity, specificity, and discrimination • High accuracy with rapid detection at minimal concentrations • Combined detection and diagnosis Library of materials properties	• Shields can respond collectively to protect groups • Shields protect across scales, from ballistic to the nanoscale • Systems responds with high confidence and low uncertainty • Sensors can be updated dynamically
Self-decontamination • Self-detoxifying materials • Electroactive textiles with the ability to control porosity (e.g., from .5 nm to 10 μm) in response to stimulus	• Catalog of polymers and crystals, including secondary and tertiary specificity • Ability to predict hybrid properties of multifunctional materials and composites • Ability to correlate material response to threat information and sensor data	Prototyping and production • Large-scale manufacturing • Nanomanufacturing is integrated into process
Library of materials properties • Build infrastructure for developing and maintaining the library • Begin to catalogue polymers and crystals for backbone structure (e.g., MOFs)	Verification and validation • Testing of systems and subsystems • Manufacturability of materials and industrial infrastructure is known Prototyping • Begin prototyping “Borg shield” systems in 2025	• Materials also used in coatings for buildings, tents, vehicles

This initiative will apply the best design tools, manufactured practices, and advanced materials and components to develop the protective gear for 2030. Some essential components for advancement to desired 2030 state for physical protection are listed in Table 3.2.

Detection and Diagnostics of Chemical and Biological Agents

Detection of the presence of a chemical or biological agent and identification of exposed individuals are complex challenges. Detection with a goal to warn individuals within a few minutes after an agent is dispersed allows action to minimize exposure. Detection with the intent to identify a treatment adds levels of complexity, with the need to identify specific agents, concentration levels, and the extent of exposure. Effective detect-to-treat strategies would provide information within hours following the release of agent to facilitate early medical treatment. At longer times, the benefits of detection can aid in the forensic identification of the source of the agent as well as determining appropriate decontamination strategies.

Detect to warn is generally easier to accomplish with today's technology. Detection of an isolated, unspecified particulate or foreign aerosol, however, is not sufficient in most cases to prompt high-regret responses such as full-scale evacuation or release of counteragents. Sensor schemes that provide some dependent capacity to confirm the dispersal pattern, to identify the agent or class of agent, or to reduce false-positives in other ways would provide much needed functionality. Nanostructures can enhance these capabilities by augmenting sensitivity levels for gas phase detection and, potentially, by monitoring living systems, such as surrogate cell lines, for physiological distress. A number of scenarios in the four worlds of 2030 are shown in Fig. 3.6.

Current program objectives for the detection and diagnostics of CB agent involve a variety of new technologies, ranging from miniaturization of existing technology to entirely new detection schemes. Miniaturization will increase portability for field use and reduce the overall logistics burden. Further size reductions will increase the sensors that can fit into a small device as well. New technologies for detection of biological agent at distances of tens to hundreds of meters are of great interest. New methods and instrumentation to reduce the incidence of false-positive and false-negative results are needed, and ideal systems will also increase the speed and sensitivity of the analysis.

Finally, it can be noted that present CB agent sensors focus on agents targeted at humans. A different set of chemical agents could also be targeted to damage structures, promoting such things as corrosion, fatigue, embrittlement, loss of adhesion, wear, or electrical failure. While the timescales and mechanisms are very different than those discussed here, there is high value in implementing additional detection capability for agents that may be targeted against infrastructure, whether military or civilian. Nanoscale sensors may enable more sophisticated detection and diagnostics in this area.

Methods

A detection scheme is a system that detects the agent, correctly identifies the agent, and defines the area of exposure. A number of different technologies are available today to detect chemical agents. Sensors are primarily designed to

Dark Empires A shipment of likely precursor for a new non-traditional chemical agent is intercepted at sea <i>en route</i> to a company in the Middle East. This is the world of Dark Empires, where state-sponsored technologies find wide application. The shipment lists a non-existent European company as the originator. US investigators note the crate has been power washed, yet several nanowire barcodes—a result of research conducted under the Cooperative Threat Reduction program—remain firmly lodged in the microscopic pores and cracks of the crate's surface. The few dozen nanobarcodes produce a strong signal that enables investigators to identify the port of origin.	Radical Game Changers A terrorist organization releases a stealth nanoparticle-encapsulated biochemical agent at eight separate airports outside of the continental US. The initial dissemination of the novel agent is undetected. Passive networks of sensors at two US points of entry, however, recognize an increase in the average elevated temperature of passengers at security checkpoints. Additional sensors show elevated levels of liver enzymes in airport waste streams. Mobile response laboratories, in coordination with National Guard Civil Support teams, are dispatched and identify the causal agent. Intensive forensics reveals that the nanoparticles are engineered to aerosolize easily and then accumulate in the human liver where they slowly release the agent. Countermeasures are administered within 12 hours. In the world of Radical Game Changers, such highly-evolved technologies require equally evolved detection schemes.
Annoying States An autonomous nanoscale gas analyzer on-a-chip planted by a U.S. agent in a teahouse in a remote mountainous region registers traces of a dual use chemical that is a known nerve agent precursor. A second nanoscale sensor planted in a nearby open-air market independently detects traces of an intermediate product associated production of the same chemical agent production. This is in the world of Annoying States, where many countries are able to perpetuate traditional offensive chemical weapons programs and crude weaponization. The information stored in the chips' memories is read remotely by a UAV on a routine patrol mission overnight. Trained intelligence analysts recognize the connection, and a Special Forces team is dispatched to the region the following night. They are able to locate a covert weapons facility and intercept a large clandestine shipment of chemical weapons.	1,000 Points of Grayness A known chemical toxin encapsulated in a nanoscale liposome— similar to the standard technology, as is characteristic of terrorists in the 1,000 Points of Grayness world, used for over the-counter herbal-supplements— is introduced into the water supply of a US city and a nearby US military installation. Because the liposomes are under 2 μm in diameter, they evade municipal mechanical filtering. As the pH is adjusted to make the water safe for drinking, the liposome shell degrades over several hours and releases the agent. The slow change in water composition is detected by a distributed biomimetic sensor network installed on the military base as part of the next-generation Guardian Program for anti-terrorism force protection and installation security. The affected supply is isolated, the incident is contained, and the water supply is remediated using auxiliary nanopore-equipped filters, which are shared with the local community.

Fig. 3.6 Selected detection and diagnostic scenarios

detect the most common chemical varieties: nerve agents; blister agents (vesicants); toxins, such as ricin; and biological agents, such as *Bacillus anthracis* (the causative agent of anthrax).

Sensing CB agents can be a complex endeavor. The simplest configuration can involve a device for transducing information about the concentration of a chemical species into an electrical signal. Such sensors can also be used to detect chemical products that indicate biological agent activity. These chemical products may be a deadly toxin or a more innocuous by-product. More complex detectors may rely on living cells with biological functionality.

A sensor array may be a set of sensors with different sensitivities and limited selectivities. Multielement sensor arrays can provide multiple data points per sample and can discriminate against interferences. The pattern of response, which is distinct for different agents, can be used to identify an unknown component using

pattern-recognition algorithms. Sensing methods available today exist with a wide variety of configurations, sensitivities, and selectivities.^{26,27}

Rapid detection – under a minute – allows military targets and first responders to recognize a threat and implement physical protection protocols. Identifying the extent of the contamination is also critical to prevent associated casualties.

Point Detection

The collection and concentration of agent is a useful and important step in the detection process.²⁸ Nanostructured materials will provide essential degrees of freedom in the construction of concentrators. The nanostructure high surface area and attendant surface modification and speed of access through interconnected porosity should enable the delivery of a highly concentrated sample of material from the concentrator into the detection volume. Examples of potential combination bio- and nanodevices include tamper-resistant, self-powered, smart nanoscale tags that can serve as covert sensors. Other applications are sensors in sunscreen, sunglasses, or garments that change color or release antidotes; and air, land, and sea dispersion of smart nanodetectors with the ability to disperse large clouds of environmentally friendly nanosensor.

The ability to detect very low concentrations of agents will always be desirable, if for no other reason than to ensure long-term exposure in a previously contaminated environment will not have consequences. For example, one of the initial symptoms of low-concentration exposure to nerve agent vapor is affected vision. This may have disastrous consequences for occupations such as fighter pilots. Nanoscale sensors have been demonstrated to detect single moieties; but, thus far, only when those moieties can be delivered to a very small detection volume.²⁹

The currently available sensitivity for gas phase sensing is acceptable, whereas a dramatic increase in selectivity is needed. Tests using nanowire arrays for gas phase sensing of NO₂ have shown sensitivity in the range of 20 parts per billion (ppb) to 20 parts per million (ppm) depending on the desired time scale – minutes to tens of minutes for 20 ppm. Other work has explored the discriminatory response of a silane-functionalized nanowire sensor array to acetone and hexane. A four-element array has shown a correlation coefficient of 0.5, which is fairly weak for four sensors. The four sensors have either no chemical modification or one of three functional groups attached: aldehyde, alkane, or amino. Current and near-term efforts will likely involve screening libraries of peptides and other organic compounds to find nanowire modifiers that can confer acceptable selectivity.³⁰

Remote Detection

Detecting and identifying an aerosolized or contaminated biological agent before contact is made is referred to as remote or “standoff” detection.³¹ With aerosols, the initial criterion for monitoring and surveillance of potential biological agent at a

distance is the observation of aerosolized masses, or clouds. At a rudimentary level, these detector types aim to alert to the presence of an approaching cloud. Depending on the situation the recipient of that alert may be military, civil authorities, public health personnel, or an individual. From that basic awareness, a more refined assessment of the contents, such as water droplets, inert inorganic material, dead biotic particulates, or nonpathogenic microbes is pursued. Ideally a standoff detector will also be able to provide some information as to the nature of aerosolized agents present.

A major difficulty in remote detection is low signal strength in electromagnetic molecular signatures. While electromagnetic wave scattering from particulates in the atmosphere makes it possible to establish their presence with reasonable sensitivity, the collection of spectral information is more difficult. Molecular fluorescence, with the strongest electromagnetic signal among the molecular spectroscopies, generally has problems with interferences. Infrared, Raman, and terahertz (THz) spectroscopies have much lower signal strength. It is conceivable that engineering of nanostructures could provide high degree of enhancements that would make them viable (e.g., silver or gold nanoparticles engineered to create highly efficient surface-enhanced Raman scattering coupled to an efficient laser light reflector to create smart dust that could be detected from an autonomous vehicle). Nanostructures will likely assist in the development of better electromagnetic wave detectors and/or improved electromagnetic wave sources. As an example, the nanoscale will likely provide improved source detection devices in the THz region of the spectrum^{32–35} (see Fig. 3.7). True remote detection implies the absence of a physical presence at the site to be probed. Because that approach is very hard to accomplish, an attractive alternative may be to seed an indicator at the site. The nanoscale opens numerous opportunities for this approach.

With the miniaturization enabled by the use of nanostructures and laboratory-on-a-chip, detection or identification devices may easily fit onto small unattended airborne vehicles.³⁶ A suspect cloud could be probed by flying the unattended airborne vehicle through it or collecting physical samples from the site. In the near term, there will be enough uncertainty in the identification such that a high-regret decision should be based on laboratory confirmation of the field measurement. The same miniaturization may enable small, low power, and easy-to-observe unattended ground stations that could serve as remote site detection or identification stations.³⁷

One example of miniaturization is flexible nanowire sensor arrays “printed” on plastic or polymeric substrates that can may be implantable or wearable. Silicon nanowires are formed using the superlattice nanowire pattern transfer (SNAP) deposition technique on silicon-on-insulator wafers (as shown in Fig. 3.8). The resulting wafer is then adhered to a poly(dimethylsiloxane) substrate, which is cured and peeled, taking the nanowires with it. The substrate is subsequently impressed onto an epoxy-coated plastic wafer and the epoxy is cured, allowing the removal of the substrate. The nanowire sensor array is thereby transferred to the flexible polymer material.³⁸ Another example for specific detection of genetic material is metallization of single strands of DNA – allowing them to conduct electricity. Based on self-assembled nanoscale circuits – using silver nanowires³⁹ or bimetallic nanowires,⁴⁰ detection of biological agents can be accomplished through DNA recognition. While this process has demonstrated high sensitivities in the laboratory,

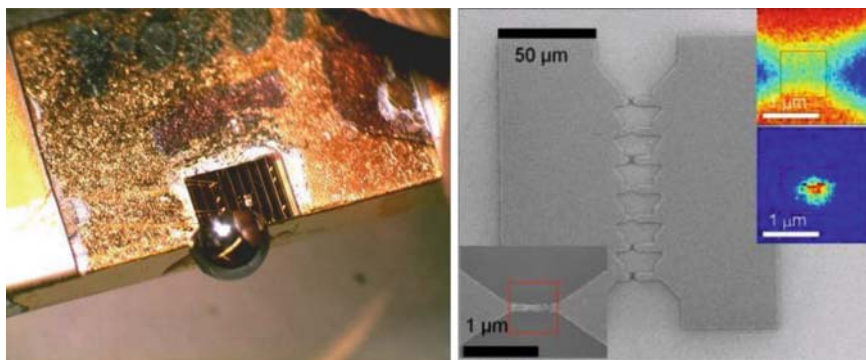


Fig. 3.7 Improvements in source detection devices in the terahertz (THz) spectrum via the nanoscale. (*Left*) First demonstrated room temperature semiconductor source of coherent THz radiation. A laser is connected to the contact pad (seen on the *left*) by two thin gold wires. A 2 mm-diameter silicon hyper-hemispherical lens is attached to the facet of the device to collimate the terahertz output. The emission frequency is 5 THz, corresponding to a wavelength of 60 μm . Image courtesy of the Federico Capasso Laboratory, Harvard School of Engineering and Applied Sciences. (*Right*) Single-molecule sensing breakthrough via simultaneous optical and electronic measurements. Rice University scientists used tiny gaps in narrow gold wires to capture electronic and optical measurements of the same molecule. Scanning electron microscopic images show the wires and gaps; *insets* are maps of optical signals from the gap. Image courtesy of Doug Natelson, Rice University

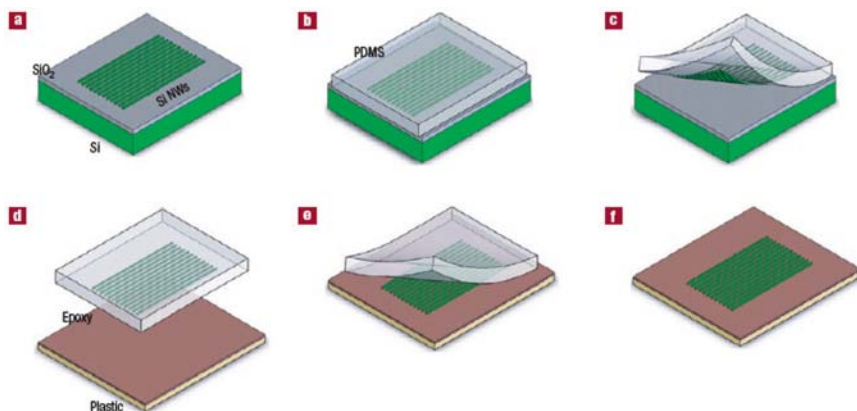


Fig. 3.8 Illustration of the steps for transfer printing SNAP nanowires onto plastic substrates. (a) Nanowires are etched into a single-crystal silicon-on-insulator substrate. (b) The exposed oxide is etched and a piece of poly(dimethylsiloxane) (PDMS) makes conformal contact with the nanowire surfaces. (c) The PDMS with adhered nanowires is peeled back from the host substrate. (d) A plastic substrate is spin-cast with epoxy. (e) The PDMS makes conformal contact with the plastic and the epoxy is cured. (f) Peeling back the PDMS leaves behind the SNAP nanowires in their original orientation, but on plastic. Image courtesy of Prof. Jim Heath, California Institute of Technology¹⁶²

it has also demonstrated increased modes of failure for nanostructured electronics – and illustrates a fundamental scientific hurdle.⁴¹ Devices based on current state of the art in metallized DNA need redundancy to counter the failure rate.

Nanoparticles incorporating gold, copper, or silver have been shown to enhance the Raman signal from adsorbed molecules as part of surface-enhanced Raman scattering. With proper nanostructure design, it is believed that the signals can be enhanced by ten orders of magnitude.⁴² An approach to seeded remote detection would be to drop nanostructured materials into the suspect site and to extract the Raman signal from a distance. Nanostructures will have the advantage of sufficient buoyancy to remain in a suspect cloud. For certain areas, the nanoscale may provide new opportunities for taggants that modify plant genetics such that overhead surveillance could detect changes in the plant characteristics when the plants have been exposed to an agent.

Chemical Agent Detection and Diagnostics

Detection and diagnostics of chemical agents presently utilizes either a visible color change indicator or ion mobility spectrometry (IMS), a variant of mass spectrometry.⁴³ Neither provides the entire range of desired capabilities for field operation. IMS is capable of detecting and identifying very low concentrations of chemicals, but miniaturizable solid state devices utilizing surface acoustic wave detection have begun to show promise.^{44–49} A surface acoustic wave device is an extremely sensitive gravimetric detector that can measure the change in mass or viscoelastic properties of coatings induced by molecular absorption (see Fig. 3.9). Based on these devices, sensor systems have been developed that can detect trace levels of



Fig. 3.9 (Left) Surface acoustic wave (SAW) resonator and (right) SAW dual delay line device (on penny). Quartz-based SAW sensors, coated with chemically selective films, can detect chemical vapors. Sensor arrays, with diverse coatings, can detect multiple chemical vapors. Image courtesy of pacific northwest national laboratory

airborne contaminants, but it is presently unable to outperform IMS. A refinement of IMS, known as field-assisted IMS or high field asymmetric waveform IMS has been explored as a potential tool for detection of chemical agents.⁵⁰

Miniaturization of both technologies is underway using nanostructures to enable an analytical chemistry laboratory-on-a-chip that will provide adequate sensitivity and selectivity against chemical (and potentially biological) agents having several inherent advantages. First, because nanostructures are both small and three-dimensional, it is possible to reduce the diffusion time for an agent moiety to reach the detection volume – presuming the sample containing the moiety can be brought into proximity of the detection volume.^{51–53} Second, the limited number of atoms in a nanostructure means that a small change can cause a significant perturbation in its properties, implying an improved signal-to-noise ratio compared to film-based sensors.⁵⁴ Third, the wide variety of nanostructures, and the new analytical tools being developed to measure or manipulate them, provides an opportunity to create new methods of discrimination. One possibility is the measurement of moiety shape or mechanical properties – variables not readily exploited in the present arsenal of analytical chemistry.^{55–58}

Mass spectrometry has been miniaturized, with present technology approximately the size of a shoe box.⁵⁹ Miniaturization onto a chip with adequate selectivity is not trivial. For example, a circular mean-free-path ion flight (and associated vacuum) will be needed to reduce overall size while preventing inelastic collisions. Nanostructures may enable better mechanisms for making and detecting ions in the continued evolution of miniaturized mass spectrometry.

Work utilizing variants of force microscopy could enable much smaller nuclear magnetic resonance (NMR) spectrometers and much greater sensitivity. Signal from fewer than 10^6 atoms has been demonstrated albeit at very low temperatures.^{60,61} The magnetic field requirements will impose volume and weight constraints even if the techniques can be further improved to permit higher temperature operation with adequate signal-to-noise ratios.

Nanoscale-enabled miniaturization of fluorescence spectroscopies – infrared, Raman, or surface-enhanced Raman – is more promising in the near term. These play a critical role in analytical chemistry by translating atomic level changes into optical signals that can be observed. One promising path to accomplish this is plasmonics – the control and propagation of light – using metallic nanostructures. Plasmonics could enable fluorescence-on-a-chip and add a powerful tool for selectivity in the detection of agents.^{62–67} Nanostructures may also be used to enhance the signal strength for spectroscopy; ten orders of magnitude gain in Raman sensitivity has been documented in select cases. Because IR and Raman suffer from relatively low signal-to-noise ratios, this gain enhancement can extend the useful sensitivity range. The enhancement of fluorescence using nanostructures has been known for over 20 years; it is only now with the growing ability to fabricate and characterize reproducible nanostructures that fundamental understanding of the phenomena is beginning to appear. With that understanding, the ability to tailor the effect to best advantage is likely to be realized.

Surface plasmon resonance can provide quantitative information on the concentration of an agent, but it has poor detection limits. Silicon nanowires, on the other

hand, are more sensitive than surface plasmon resonance by orders of magnitude. If binding rates (k_{on} and k_{off}) are known for a biomolecule, it is possible to quantitate concentrations in physiologically relevant environments. Few mass spectrometry techniques in development have such capabilities.

In addition, a wide variety of innovative detection techniques are under development using micro- and nanoscale devices. An important opportunity in point detection will be to leverage progress being made in nanodevices for other applications. A few of these are illustrated below:

- Microfabricated cantilevers, developed for atomic force microscopy, can be used to indicate adsorbed molecules in a number of ways: stress, weight, energy release.^{68,69} Mechanical deformation of the cantilever is detected by optical reflection or piezoelectric voltage change. The cantilevers have been microfabricated in arrays of thousands, which could enable pattern recognition approaches to selectivity. Interestingly, a cantilever assembly has been shown to detect the presence of high explosives as well as CB agents.
- Interdigitated electrodes, bridged by electroactive materials, can detect small changes in electrical conductance; this assembly is frequently referred to as the “chemiresistor.”^{70,71} Selectivity is provided by utilization of different nanoscale materials.^{72–74} Working at the nanoscale makes a useful range of resistive materials available.
- Filling the volume between interdigitated electrodes with nanostructures separated by thin electrically insulating films provides added functionality. As molecules adsorb into those films, the nanostructure separations are modified, inducing measurable changes in the tunneling current.
- Semiconductor nanowires provide very sensitive detectors, where adsorbate-induced charge separation can convert an entire silicon nanowire into an accumulation or depletion zone.⁷⁵ The same adsorbate on a macroscale silicon surface would induce only a surface layer but leave the bulk unaffected. The main problems to date with nanowires and their assembly are quality control; a number of research endeavors are currently aimed at exploiting nanowires for detection and overcoming these technical challenges.⁷⁶ Groups at Caltech and the Naval Research Laboratory have independently been pursuing innovative technical solutions to these problems.^{77,78}
- Nanoparticles in the form of quantum dots are reaching a mature stage in the development of medical applications.^{79–84} Their fluorescent yields are in the visible and infrared. They outperform organic dyes in the narrow emission linewidths, they have the capability to excite a wide range of useful emissions with a single ultraviolet (UV) excitation, and they are resistant to photobleaching.
- Nanoporous silicon, made by nanoetching or a hydrogenation/dehydrogenation process, has demonstrated metastable simulated light emissions and may be useful in various sensor applications. It may also be a biocompatible material with tailored biodegradation.^{85,86}
- Nanoscale memory elements created for radiation hard, non-volatile memory (using gigantic magnetoresistance technology) have displayed sensitivity to the

paramagnetic beads used to collect biological molecules in solution. Nanoporosity is being utilized to separate and identify biologically relevant moieties.^{87,88} It may be possible to adapt these techniques, which utilize sandwich assays of biological molecules, to the smaller chemical agent molecules. If successful, the same sensor might be utilized for both chemical and biological agents.

The incorporation of these new “spectroscopies” into a laboratory-on-a-chip will be essential for adequate selectivity.^{89–91} Considerable progress has been made toward the development of microfabricated sensor arrays, where each element in the array is capable of its own preselected detection event, but the technology is not sufficiently robust to place into field operation.^{92,93}

Whether utilizing multiple spectroscopic techniques or array technologies, pattern recognition software (or firmware) will be needed. Without this more sophisticated analysis tool, it will be impossible to achieve the desired selectivity and quantification.

Biological Agent Detection and Diagnostics

On the biological side, wet chemistry remains the driving factor in the ability to detect and identify the threat. At present, the potential number of new and emerging threats (naturally occurring or man-made) is far outstripping the ability to identify the threat irrespective of developing medical countermeasures. Technology from the medical and genomic communities has pointed in one direction toward developing the capability to do complete pathogen nucleic acid sequencing. Such new sequencing capability would need support from the bio-informatics community.

The goal of much of the recent federal investment in biological detection has been to provide a real-time capability to detect, identify, characterize, quantify, locate, and warn against all known or validated biological agent hazards, including emerging natural disease agents and genetically engineered agents. Sensors for the individual warfighter or first responder and systems capable of detecting multiple agents and characterizing new agents are being developed. Advances in technology are being pursued for biological standoff detection, early warning detection, miniaturization, and interconnectivity; enhancements in detection sensitivity, rejection of interferents, logistics supportability, and affordability are also being addressed. The increased lethality and heightened operational tempo of future battlespaces demand responsive detection and warning capabilities.

Field equipment is available that is capable of identifying liquid droplets on surfaces and in vapors. Laboratory-based equipment can further detect agent in water, food, and blood. One of the main challenges with these schemes is ensuring an appropriate sample for analysis and filtering out nonhazardous species present in the environment.

For diagnostics, the “gold standard” for identification of microbiological species remains culturing – literally growing a colony of microbes on a nutrient containing surface in a Petri dish and observing it with the eye or through a microscope.

Culturing is inexpensive and highly sensitive but slow. Roughly a minimum of a million (10^6) bacteria are necessary to form a visible colony. Detection of single cells is possible but only after long incubation times, typically days. Typical evaluation times are 12–24 h for many bacteria but can exceed a week for exotic, slow-growing, or more difficult to culture agents. Immunoassay-based detectors use processes found in the human body's natural immune system. The immune system produces highly specific proteins, called antibodies in response to antigens from foreign bacterium, toxins or other microbiological organisms. Antigens are molecules on the surface of the foreign microbes. Antibodies form strong and specific interactions with antigens. This specific response is the foundation of immunological detectors.

Emerging array-style monitoring techniques can allow multiparameter detection. One such technique used for marker monitoring and cell sorting is the use of DNA-encoded antibody libraries, capable of rapid serum analysis with extremely high sensitivity – femtomolar range is possible. Also, chips can be more readily prepared and stored. When used within rapidly flowing microfluidics channels, assays can be executed in a few minutes – vs. hours characteristic of other methods – on trace amounts of sample, less than 10 μl .⁹⁴ This level may not be obtainable for all measurements, but enables good serum analysis.

To improve diagnosis and response, it is necessary to further increase a broad range of measurement capabilities, including the ability to measure more than one parameter simultaneously, improved quantitative methods and specificity. The ability to implant or wear the sensor is also highly desirable.

Biomolecular sensors utilizing ultrahigh-density nanowire circuits can fill this need. Silicon nanowires can allow scalable real-time sensing with a dynamic range of 10^6 and sensitivity in the 100 attomolar range (10^{-18}). In such sensors, protein-capture agents such as antibodies are located along a nanowire; when a protein binds to the agent, the complex acts as a field effect transistor and induces a measurable change in the conductivity of the nanowire. Efforts to modulate or improve the sensitivity range have included using different types of silicon. Tuning the dynamic range of silicon nanowire sensors is also possible by chemically modifying the surface of the nanowires.

Potential Improvements in 2030

It is likely that future systems will use nanoenabled hardware components to accomplish the 2030 goals and reduce the physical and logistical burden of future detection platforms. Components under development include nanoelectronics^{95–98} or nanophotonics^{99–103} and nanotechnology-based energy devices that convert ambient energy – thermal, vibrational, or ambulatory – into electrical energy.^{104–108} Research in basic and applied nanoscience will be needed to take detection platforms from vehicle mounted to suitcase size to embedded autonomous sensors in vehicles or uniforms.

Detection and diagnostics of chemical or biological agents is not just an engineering exercise for performance enhancements. Regardless of the size, complexity, or deployment of detection systems, the basic questions remain: What chemical or biological signatures can a system detect? It is currently unclear how far nanoscience will be able to enhance the basic sensing element needed to recognize distinct molecules. To this point, carbon nanotubes have been shown to sense and differentiate such gases as ammonia¹⁰⁹ or nitrogen dioxide¹¹⁰ by measuring changes in resistance across the nanotubes. In most cases nanomaterials themselves are either nonresponsive or nonspecific to chemicals or biochemicals. To develop a sensing element, additional basic and applied research efforts in understanding and designing surface functionalization for molecular recognition is essential in the near term. Carbon nanotubes coated with single strand DNA (ssDNA), for example, have been tuned to sense different vapors such as methanol, dimethylmethylphosphonate, and dinitrotoluene by choosing the appropriate ssDNA base sequence.¹¹¹ Carbon nanotubes doped with metals such as boron¹¹² or zirconium oxide¹¹³ display enhanced specificity or sensitivity of chemical or gas detection. Polymer-nanomaterial composites are yet another way of functionalizing nanomaterials for selective detection.^{114–117}

Current approaches to detection and diagnostics of biological agents are based on threat agent identification using agent-specific DNA sequences, antigen–antibody interactions, or analysis of biological activity. To reduce their size, these DNA sequences can be hybridized and antibodies or bioactive enzymes can be tethered to nanomaterials – carbon nanotubes or gold, silver, or silica nanoparticles (see Fig. 3.10).

Unfortunately, small is not enough, and improvements in detection schemes are also needed. For example, an anthrax-based attack could be released simultaneously with an immunomodulator that responds to antibiotics used to treat the patient. When an individual exposed to this anthrax cocktail is given antibiotics, the immunomodulator may cause overstimulation of the patient's immune system and result in rapid death. A single-aspect detection scheme may only identify the anthrax and ignore the immunomodulator. This is true regardless of whether the system is macro-, micro-, or nanoscale.

Although the release of such a binary biological agent may seem far fetched, one only needs to consider the overwhelming funding for nanotechnology aimed at medical and pharmaceutical research. The use of nanotechnology in drug delivery shows tremendous promise for targeting specific individuals, specific organs, and even specific cells. Nanotechnology research is also advancing aerosolization of drugs and nanoparticles as drug delivery mechanisms. These techniques can increase drug bioavailability and decrease drug degradation and harmful side effects. Nanotechnology methods have also opened many potential avenues for designing drug carriers via drug encapsulation, including silica spheres,¹¹⁸ liposomes,¹¹⁹ or biodegradable polymers.¹²⁰

Specific tissue can be actively targeting by tethering cell-specific recognition functional groups, or moieties, to nanoparticle surfaces impregnated with drugs. It is clear that the same techniques and technologies targeted to improve medical care could be used for maleficent use in delivery of harmful agents. These may include

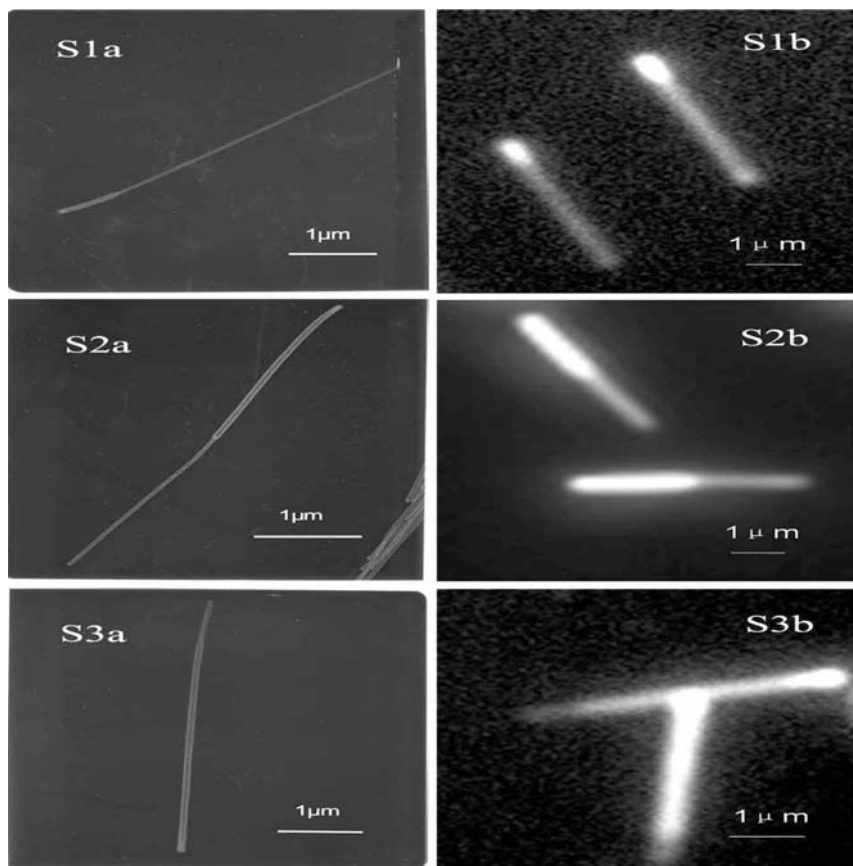


Fig. 3.10 Shape-differentiated silica nanotubes for biosensing. Silica nanotubes can be externally and internally functionalized. Compared with the conventional microarrays on a plate, the suspended nano/microarrays may offer greater flexibility, faster reaction rate, greater reproducibility, less consumption of sample and reagents, and thus higher sensitivity. Image courtesy of Prof. Sang Bok Lee, Department of Chemistry and Biochemistry, University of Maryland, College Park, MD

simple or binary chemical or biological agents, toxic industrial chemicals, or nontraditional agents, and could be aimed at the human population, agriculture, or other economic or iconic targets.

Many traditional detection approaches would fail to detect such nanoenabled threat agents. Further, research in synthetic biology currently aimed at creating new viruses, cells, and organisms is another path that could produce unknown pathogens. These trends in biotechnology and nanotechnology for medical and pharmaceutical applications are only some of many reasons why new understanding of detection and diagnostics is needed in this evolving technological realm.

Nanoenabled technologies offer some inherent advantages for CB agent detection and diagnostics at all levels.^{121–126} Foremost, the innovative properties of

nanostructures can be exploited for the transduction of a chemical agent reaction into a discernable signal.^{127–129} Instrumentation developed to maximize signal with minimal noise via nanotechnology may provide new ways for detection and discrimination of CB threat agents.¹³⁰

Further, miniaturization beyond microelectronics and MEMS may facilitate the development of array detectors that provide expanded functionality per unit volume. Such arrays will be necessary to provide adequate selectivity, meaning an acceptable level of false-positives and false-negatives, in addition to adequate sensitivity. It is a near certainty that adequate selectivity for chemical threat agents will require the measurement of more than one physical or chemical property of an agent. By analogy, when presented with an unknown substance, the analytical chemist will use a suite of tools – separation technologies, mass spectrometry, optical spectroscopies (infrared (IR) and Raman), and nuclear magnetic resonance (NMR) – to develop a definitive identification. It is unrealistic to expect that the development of small, portable detectors based solely on the measurement of a single property will outperform a stable of full-sized sophisticated instruments. Miniaturization, while sure to degrade the state-of-the-art capability found in a full-scale instrument, will also allow combinations of instruments utilizing small volumes and little electrical power. The nanoscale will enable the continuation of microtechnology advances, and the concept of laboratory-on-a-chip can be realized. Small-scale array detection based on microfluidics principles may also provide the opportunity for integrating CB detection and diagnostics into the same systems.^{131–133}

Presymptomatic Disease Detection and Diagnosis

An ideal countermeasure to a world of asymmetric or unknown bioenabled threats will prevent any impact to individuals. In one scenario, an infection can be detected and the causative agent or agents characterized prior to the onset of symptoms. In a different scenario, a new virus may be synthetically derived and therefore difficult to identify. The host's response to that novel microbe may indicate a course of treatment before the agent can be identified.

Two potential avenues of research are identified for presymptomatic disease detection and diagnostics. One approach is to increase detection sensitivity and speed for isolating causative agents during the early phases of replication in the host. Another approach is to characterize a host's molecular response to infection through the identification and characterization of early stage molecular signatures. It may be possible to use the host's molecular response to differentiate, for example, a bacterial infection from a viral infection or one viral infection from another.

Artificial Immune System

Moving from advancements in current approaches to sensing and detections, one vision for 2030 is the use of an artificial immune system as a detector. Immune

system biology for CB defense generally refers to the medical countermeasures, prophylaxis, or pretreatments. Sensing and detection countermeasures for biological agents for 2030 worlds will be designed and constructed on with capability to respond to threat agents of unknown genomic composition, virulence, or delivery. One approach to realize such detectors is via an artificial immune system.

The immune system is an autonomous cellular network responsible for defeating pathogens and discriminating between self and foreign microbes. It is composed of two systems, the innate and adaptive immune systems. These have independent and unique functions, yet communicate to accomplish the mission to defeat the foreign invader. The innate immune system is an immediate and nonspecific defense mechanism that the host intrinsically uses to eliminate microbes and prevent infection. An innate immune system is found in all classes of plant and animal life. The adaptive immune system is the second line of defense, requiring activation and time to react. It is highly specific for a given pathogen and maintains a memory of that pathogen by generating antibodies against specific antigens to prepare the body for future attacks.

Today, many detection and diagnostics systems mimic the adaptive immune system. They use agent-specific recognition elements in immunoassays such as antibody–antigen interactions or specific genomic sequences that hybridize to their complement strand. These approaches are used to “identify” an agent and are not designed to sense the presence of foreign or harmful microbes. Sensing requires the ability to discriminate between host cells, beneficial or commensural microbes, and harmful or foreign microbes. The innate immune system is the sensing component.

Mimicking processes in the innate as well as the adaptive immune systems have the potential to connect a capability of nonspecific sensing to the very agent specific mechanisms. Living systems present a number of defenses when contacted by a threat agent, whether intentionally genetically engineered, naturally occurring, or nanoencapsulated. The body’s protective system is composed of skin, mucous membranes and epithelial cells in the eyes, nose, mouth, throat, lungs and phagocytes. These layers differentiate self from nonself through an array of parallel, sequential, orthogonal, and redundant chemical and biochemical signaling interactions.

The innate immune system is continuously under asymmetric attack by microbes and chemicals from the environment.¹³⁴ The system baselines chemical and biochemical signatures through highly multiplexed arrays in order to sense an anomaly signature and mount a counter attack.

The innate immune system is not a simple cell type; it is a key component in many tissues in the respiratory tract, gastrointestinal tract, the reproductive tract, and the vascular system. While cellular-based systems may be desired as sensors, logistically, cell-based sensor systems are living organisms and may require burdensome maintenance in the field. For these reasons, the ability to mimic sensing mechanisms and processes with engineered or synthesized materials has the potential to create a robust and field-deployable sensing array. Realization of such a countermeasure will require multidisciplinary work across the fields of molecular biology, biochemistry, and nanotechnology. Information and computer sciences will be important as well, including new artificial intelligence systems, algorithms, and integration.

Pathways to Achieve CB Countermeasures

Conceiving a new technology is only the first step. As an example, the concept of a laboratory-on-a-chip has been slowly evolving – in some ways more slowly than expected – over the past 10 years. The slow pace has been attributed to the lack of a driving application, meaning one with an undeniable payoff that would focus the necessary resources and innovation. Examples of driving applications and the necessary underlying capabilities are discussed here for CB countermeasures.

Determining Core Capability Requirements

Determining the needed core capabilities can be aided by examining the fundamentals of sensing, detection, characterization, and representation of physical phenomena. Broadly, sensing can be defined as the ability to discern that “something is different” in a given situation or environment. This is also known as anomaly detection. Anomaly detection is not agent identification; rather it is the observation of events that rise above the normal background. As such, it requires continuous monitoring of a baseline signature with a goal to recognize the normal, albeit fluctuating, physical, chemical, and biological environment. In a world of unknown CB threats and nanoenabled threats, future threat agent sensors must be designed to sense anomalies from any source, be it in the laboratory, the clinic, or the larger environment.

Sensing in biological systems occurs in nature through detecting and responding to a complex and multiplexed array of distributed molecular processes. Critical specificity is needed in a world where bio- or nanoenabled threat agents are designed to defeat biological systems and disrupt normal cellular and molecular processes. When such agents invade living organisms, they cause a cascade of molecular changes that appear as anomalies to normal processes. Effective sensing in this environment will mimic biological processes. Such biomimetic systems would therefore be modeled upon the methods and systems found in nature.

Stepping from conceptual to sensing technologies in the real world is not a simple transition. The system is not a single cell but systems of many types of cells. Anomaly detection in multiplexed arrays of autonomous distributed networks requires massive amounts of parallel and orthogonal information processing, including real-time data mining, data synthesis, and data transmission. Sensors designed for anomaly detection that integrate these technologies may provide high fidelity answers through nonspecific information. When more specific information is available, additional capacity must be utilized, including rapid molecular discrimination, characterization, and quantification. These are essential to communicate risks to the public, to discern appropriate medical countermeasures, to inform forensics for attribution, and to determine appropriate decontamination processes.

Biomimetic sensing and rapid molecular identification and characterization are not revolutionary concepts. They are as much a desirable attribute today as they will be in the future. To be most effective, research on these core capabilities should

include methods for sensing unknown agents and unknown delivery mechanisms in addition to traditional agents and dispersal.

The following concepts summarize the focus for research and technology development for detection and diagnostics of CB agents across all of the potential world futures.

- Biomimetic sensing through anomaly detection
- Autonomous massively multiplexed sensor arrays
- Autonomous distributed networks
- Rapid molecular discrimination (identification and characterization)

Technology Opportunities

A potential application to drive technology development is a point detector simultaneously capable of sensitive and selective detection and identification of both chemical and biological agents. Technical problems in building such a device include the following:

- More effective micropumping mechanisms and sample collection
- The incorporation of high performance electronics for signal processing onto flexible and conformed substrates
- Processing adapted from MEMS technologies extended to materials other than silicon, such as mylar, polydimethylmethyl methacrylate, and polycarbonate

Present chemical detectors utilize a single transduction mechanism – colorimetric change or ion mobility (a variant on mass spectrometry). Current microfabrication technologies already enable the development of arrays that incorporate more than one transduction mechanism. There should be a program to foster the development of such arrays in the near term. The use of array technology implies the necessity for pattern recognition to best extract quantifiable conclusions, so adequate computational power must be included on the chip. The development of approaches to scavenge power from the environment could significantly extend the operational lifetime of such chip.^{135–137}

The transduction of the presence of a single agent moiety has been demonstrated many times – provided that moiety is precisely in the right location. That translates into a major challenge for sample collection and processing. At the nanoscale, where diffusion distances are not very large, there still remains the problem of delivering the agent. While diffusion distances are reduced in the small channels in a laboratory-on-a-chip, turbulent mixing is still useful. This poses a challenge to microfluidics that tend to operate under laminar flow conditions.¹³⁴

Nanoscale particles in the air present safety and health concerns in the manufacturing environment; this issue is being carefully examined and solutions are being developed.^{138,139} It might be possible to exploit advances in detection or filtering of nanostructures for the collection of CB agents. Nanostructures are sufficiently buoyant to minimize gravitational settling, but they can be produced with dielectric

or magnetic properties that provide a physical “handle” for their manipulation.¹⁴⁰ Micrometer-sized paramagnetic particles are in use by immunoassay techniques; they are physically stirred through a liquid media to come into contact with substrates of interest and then attracted into the detection volume by magnetic field gradients.¹⁴¹ Electrostatic precipitators are utilized to extract dust particles from the air. These concepts might be extrapolated into the nanoscale to enhance collection efficiencies.

Nanostructured adsorbents could play an important role in sample concentrators. The high surface area of nanostructures would provide ample opportunity for improved adsorption. Equally important, properly designed porosity could minimize the transport time intervals of desorbed entities. Nanostructures have been demonstrated to penetrate a highly concentrated plug of a sample agent in a short time span. Nanoscale porosity might also play a role in separation processes in sensor systems.¹⁴²

In addition to traditional CB agents, new insights into the blood–brain barrier may provide new opportunities.¹⁴³ As our understanding of brain function grows, there may be an opportunity to influence human decision processes by the introduction of chemicals into the brain.¹⁴⁴ If this were to happen, a means to detect those chemicals will be paramount.

The artificial immune system and presymptomatic disease detection are 2030 envisioned countermeasures that require focused integration via development of strong interdisciplinary research teams – involving chemistry, physics, engineering, computer science, biological sciences, mathematics, or informatics. The emerging disciplines of systems biology, synthetic biology, informatics, and materials sciences such as regenerative materials, molecular amplification technologies, biocatalysis, reagentless sensing platforms, multifunctional “smart” materials, and nanoscience are some of the key areas of research requiring significant investment. Table 3.3 lays out a roadmap of essential science and technology components from today through 2030 to achieve the desired 2030 countermeasures to biotechnology and nanotechnology enabled threat agents.

New Fields and Capabilities

The field of microfluidics, based on the extension of silicon-based MEMS technology, needs to be extended into the use of nanofluidics and nanostructures incorporated into microfluidic channels.

Functional nanowires, especially those incorporated into microelectronics, provide multiple possibilities for improvements in sensitivity and selectivity of CB agents.¹⁴⁵ They also offer the prospect for high performance electronic circuitry fabricated at lower temperatures and on flexible substrate materials. Because sensitive and selective CB detection will likely require some form of pattern recognition, the ability to incorporate the detection transducer with reasonably sophisticated electronics is a necessity. Implicit in that statement is the need for the transduction ultimately to provide an electrical signal (as input into transistor-based computation).

Table 3.3 Essential components for advancement to desired 2030 state for detection and diagnostics

By 2010	By 2020	By 2030
Chemical	• Biomimetic/single cell/ tissue-based sensors, instrumented cells (nanocanary), e.g., B-cell sensors	• Tamper-resistant, self-powered, smart nanotags; covert sensors; sensors in consumer goods, dual-purpose sunscreen, sunglasses, garments that change color and/or release antidote
• Distributed networks	• Implantable sensor devices with presymptomatic sensitivity to biomarkers	• Air, land, and sea dispersion of smart nanodetectors, ability to disperse
• THz for single molecule detection/illumination (or other parts of spectrum, perhaps as complement) already ongoing to some extent. May need to use in concert with something else to enhance fidelity. Enabling technologies in process (able to mix and match by 2030)	• Tamper-resistant, smart nanotags, self-powered covert sensor deployment, e.g., embedding sensors in consumer goods	• Biomimetic/cell/ tissue-based sensors, instrumented cells (nanocanary), e.g., B-cell sensors implantable sensor devices with presymptomatic sensitivity to biomarkers
• Combinatorial - electrochemical, piezoelectric, etc.	• Standoff detection of suicide bombers and “gassers,” human stress response indicators	• Engineered seeds and genetically-adapted crops replicating detectors for global monitoring of threats
• Miniaturize mass spectrometry, lower power with a more robust system	• Electronic nose sensors/ sensing systems	• Synergistic “lab on a spec”, e.g., no macroscopic analog
• Massively multiplexed assays	• Responsive/reactive skin coatings/accessories, dual-purpose sunscreen, sunglasses, garments that change color and/or release antidote; air, land, and sea dispersion of smart nanodetectors; specific response, talk-back capability; ability to disperse large clouds of nanosensors	• Cell/tissue in vitro or in vivo sensing will detect, identify, and destroy the particle. Provide info on the bio-response, biomarkers, etc.
• Combinatorial technologies/ integration of multiple technologies– microfluidics and electronics	• Engineered seeds and genetically-adapted crops replicating detectors for global monitoring of threats	• Detect the impact on biosystems by responses. Environmentally distributed nanoparticles will have a detectable signature. Components of lab on a spec may be possible
• Wiring superimposing photonic arrays on light-emitting transistors	• Synergistic “lab on a spec” hidden in a commercial device	• Detect delayed clinical expression of disease, i.e., “mad cow” disease. Entry point is a vulnerable food chain.

(continued)

Table 3.3 (continued)

By 2010	By 2020	By 2030
Biological	• Scale energy sources to nanoscale	• Detect remotely activated; no apparent hazard or threat, need more effective biomimetic sensors, protective suit that will block or inactivate a threat challenge
• Targeted attachment of molecules and/or functional groups to nanostructures • Demonstrated autonomous motion in nanoparticles	• Biotic/abiotic interface, e.g., robust transduction method • Analytical tool/techniques for nanoscale	• Detect self-replicating biothreats that deliver toxins • Detect co-opting commercial materials or commonly used technologies, i.e., cosmetics for stealth detectors
• Blood/tissue sensor interface	• Robust, controllable, reproducible manufacturing techniques for nanodevices	
• Demonstrate a robust, passive nanotag	• Library arrays of known characteristics, signatures	
• Biological threat recognition and identification	• Interfaced in vitro cellular systems (identifies the molecular cascades that occur in response to exposure)	
• Biomimetic systems as nonspecific indicators of threat and response	• Artificial immune system – must understand the chemistry/biochemistry of sentinels – diagnostics of environmental exposure systems	
• Nanocanary	• Systems Biology, including: library of host responses to pathogens; library of pathogen responses (metabolic pathways) to handling	
• Monitor human blood chemistry for diagnostics (in vivo or in vitro)	• Rapidly ability to identify an unknown (<i>how do you know what you don't know?</i>)	
• Implantable sensor nanodevices	• Understanding to translate to multifunctional nano-based materials designed to “mimic” biological systems	
• Drug delivery, implanting marine proteins into cell walls for therapeutics	Synthetic Biology	
• Biological filters	• F(3) Find, fix, finish	
• Biomimetic chemical or toxin sensor arrays	• More portable, more fault-tolerant	

(continued)

Table 3.3 (continued)

By 2010	By 2020	By 2030
• Harnessing biological systems for other processes, i.e., energy source	Social informatics • Advances in epidemiology • First responder detection/point of care diagnostics/presymptomatic diagnostics • Nanoenabled sensing environments will be more common • Rapid forensics for attribution • Rapid detection with fewer false alarms • Mass production • Molecular amplification technologies • Nanocatalytic technologies and regenerative materials	

In the future, as photonic signal processing progresses, pattern recognition could also be based on photons.

Current chemical agent detectors are tailored to detect known agents. The ability to detect new threats is equally important. A detection technology based on the detection of environmentally induced changes in cell or tissue physiology would provide a “canary on a chip”. The incorporation of living cells or tissue with semiconductor devices to form a detector based on cellular response to environmental stress has been demonstrated.^{146,147} Some remarkable examples have recently been demonstrated that utilize functional nanowires to sense/interrogate action potentials from nerve cells grown on a silicon wafer.¹⁴⁸ Major issues are expected in dealing with cell lifetime and stability and in enabling better extraction of signal transduced from a variety of environmentally induced changes to cell physiology.

The ability to sense human body physiology *in vivo* and in real time would provide the opportunity to take the canary on a chip concept to the next level. The physiological response of the individual could be monitored. The early onset of changes to body chemistries could be detected, with an alarm and/or corrective action initiated. Beyond CB-agent-induced stress, such a system could also monitor for fatigue and other debilitating effects. Rudimentary versions of such capability are already in the medical market for diabetes. Some essential components for advancement to desired 2030 state for detection and diagnostics for CB agents are listed in Table 3.3.

Decontamination

Effective decontamination of military personnel, first responders, exposed civilians, equipment, and infrastructure remains a technical and practical challenge. While avoiding contamination is a first priority, it is not always possible. Tools are needed to neutralize hazards after CB threats have been deployed. Technologies such as sprays, mists, and dispersion methods, coatings and catalysts, and various types of washing and physical removal will be appropriate for different decontamination operations. Decontamination science and technology is targeted to carry out this mission while minimizing damage or degradation to the people, environments, and equipment involved. Technologies should therefore be noncorrosive and environmentally safe. A number of scenarios in the four worlds of 2030 are shown in Fig. 3.11.

Critical issues for decontamination that need to be adequately addressed for both military and civilian application include agent absorption into porous materials (e.g., concrete, wallboard, polymeric materials) and the challenges this poses. Validating the fate of low-level biological and chemical agents inside buildings and other structures also remains difficult. Sample collection efficiencies need to be

Dark Empires While on an expeditionary flight in the world of <u>Dark Empires</u>, a returning B-2 Bomber flies through what initially appears to be a swarm of insects. The material is actually a suspended aerosol of a super-corrosive, super-acid based anti-material agent, which has properties deleterious to humans. As the plane lands, initial sensors indicate the presence of an unknown compound. Selective nanoporous decontaminants are immediately applied to plane's surface inhibiting subsequent degradation of the surface without interfering or harming the sensitive electronic components as well as detoxifying the chemical threat.	Radical Game Changers At an embassy function in an oil-producing allied state, a contracted catering company is infiltrated by individuals opposed to US presence. In this world of <u>Radical Game Changers</u>, all utensils and plates are coated with a translucent biofilm containing a genetically-engineered percutaneous toxin. An astute young Army Chemical Corps officer initiates testing on a next generation hand-held PCR-like device... but not until after the ambassador, her family, and distinguished guests of the foreign state have contacted the contaminated utensils The embassy . has recently been selected to receive a beta-version of nano-engineered decontaminating solution intended for post-exposure treatment of skin and mucous membranes. These "nanosponges" bind the toxin without reacting deleteriously to the skin. Once isolated in the 'nanosponge,' the materials react with ultraviolet light to degrade the toxin.
Annoying States A team of soldiers encounter stockpiles of chemical weapons. In an <u>Annoying States</u> type world, these caches hold munitions containing weaponized sarin and other third generation nerve agent munitions. (In a world of <u>Dark Empires</u>, the stockpiles hold advanced non-traditional agents and emerging novel biochemical agents that challenge even highly advanced countermeasures.) The soldiers are equipped with decontaminating sprays which coat the boxes, crates and barrels with nanoparticles that passivate the surface. A second spray-on material "shrink wraps" the stockpile until the "WMD Elimination and Site Exploitation" team can be deployed.	1,000 Points of Grayness At rush-hour on a Friday evening in January, a half-dozen improvised chemical devices (ICD) detonate in subway stations in Washington, DC. They produce a hazardous of cyanogen chloride, which dissipates very quickly and affects only a few riders. Nonetheless, placement in crowds with limited egress results in a 'worried well' syndrome of those exposed and over 5,000 citizens demand treatment. A nanoparticle-based cream is distributed that serves as a non-toxic topical decontaminant. The devices, easily constructed from commercially-available materials, are readily-concealable and blend in with their surroundings. This takes place in the world of <u>1,000 Points of Grayness</u>.

Fig. 3.11 Selected decontamination scenarios

better understood with different methodologies on relevant indoor surfaces. Another fundamental research area is faster and more accurate methods to predict and understand physiological response to traditional and emerging agents, including low-level toxicology effects. In the civilian sphere, much more accurate information is needed regarding toxic loads and reliable concentration data for acute and long-term exposures for the general population.

Postexposure Protection and Decontamination

To protect the warfighter from current and potential future “super-toxins,” the threats should be described with as much technical precision as possible. Future threats may include more sophisticated CB weapons but also entities such as prions (as “weaponized” proteins) or toxic nanoparticles.

The targets of toxic material must also be considered. If personnel or animals are targeted, countermeasures must be relatively benign, safe to handle, and reasonably safe for the environment. Simultaneously these countermeasures must also be effective in a chemical reactivity sense; they must (1) *destroy* the chemical or biological agents, which is frequently via chemical means such as by destructive adsorption of another toxic chemical or destructive; (2) *kill* a biological agent by altering the biochemistry or removing the outer protective coating of the virus, vegetative bacteria, or spore; (3) *neutralize* the toxic agent, whether it be by strongly adsorbing the toxic chemical, virus, bacteria, spore, prion, or deleterious nanoparticle, or by physically trapping the agent.

One novel application of nanoparticles for neutralization would be for an environmentally safe nanoscale material that could settle and adsorb onto the surface of a dangerous spore, such as anthrax. The spore would not be “killed,” but if the spore germinates, the vegetative cell is susceptible to the nanoparticle. Indeed, the spore–nanoparticle adduct pair may exist for years, but in effect, the danger of the spore has been greatly diminished. Current nanotechnology research that may be leveraged include “anti-anthrax nanosponges” that bind the bacteria’s lethal and edema toxin and render them ineffective¹⁴⁹ or adapting work on temperature-stable nanoemulsions currently being developed as vaccines,¹⁵⁰ as “pathogen avoidance” barrier, and topical postexposure reactants for the skin and mucous membranes.¹⁵¹

The protective nanomaterial envisioned should be engineered in such a way that it exhibits the desired chemical reactivity, shape, light sensitivity, and electrochemical sensitivity. To rationally design the desired nanomaterial properties, one must also have a fundamental understanding of how threat agents are neutralized or destroyed. Otherwise, development of nanomaterials for agent neutralization or destruction becomes one of trial and error. To gain this fundamental understanding for chemical agents, one can conduct computational chemistry (quantum) modeling and experimentation of the hydrolytic and oxidative mechanisms and reactions for chemical agent decontamination, leading to new and fruitful decontamination

development directions. Research path priorities identified by this basic research can be pursued to develop advanced chemical agent decontamination technologies.

A goal is to build functionality into a material at the nanoscale and microscale such that multiple toxic compounds can be decontaminated. In the future, nanomaterials with multiple chemical reactivity sites (Lewis acidity, super acidity, Lewis basicity, strong basicity); reduction oxidation (“redox”) catalytic properties (stored oxidative and/or reducing capability); controlled pores (sizes, shapes, chemical properties); light-absorbing properties (photocatalytic and photocatalytic oxidation using ambient air); electromagnetic radiation absorption; and electrochemical properties (for conduction and electronic information transmission) will be possible. Figure 3.12 shows desired properties to be incorporated into such a material.

It has been demonstrated that, as the crystals of a solid, inorganic substance (e.g., MgO , Al_2O_3 , or SrO) become smaller and smaller, shape changes occur.¹⁵² The secondary structure, or the aggregates of the nanocrystals, changes from weakly adhering big cubic crystals to smaller platelets, and eventually, for the smallest nanocrystals, to a fiberlike mesh. For example, see Fig. 3.13 for magnesium oxide. Note in Fig. 3.13d how pores have formed in the nanoscale range. These pores can serve as traps for molecular toxins. Also note Fig. 3.13c where larger macropores are shown within a fiberlike “cottonball” aggregate structure. Such pores can serve as traps for bacteria or viruses, and the walls of the pores are made of a reactive form of an otherwise environmentally friendly material, nanocrystalline MgO .

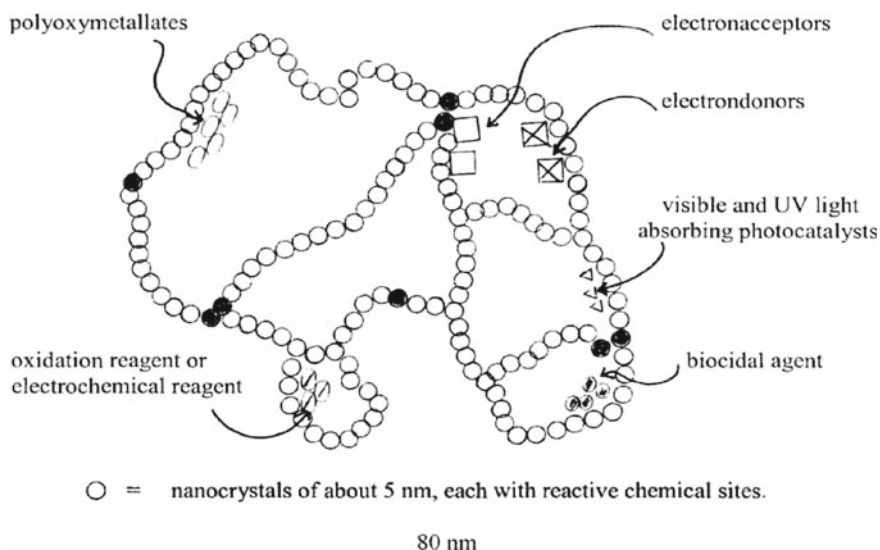


Fig. 3.12 Cartoon illustrating desired properties for future nanomaterial for decontamination¹⁶³

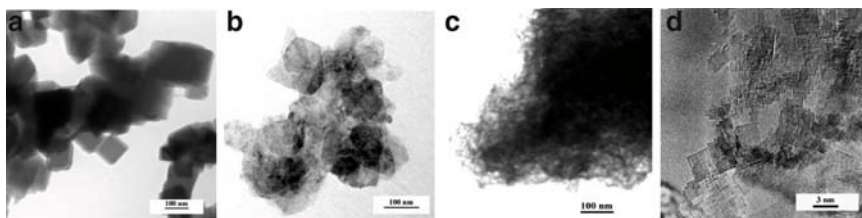


Fig. 3.13 Morphologies of nanocrystalline materials varies, as shown in TEM images of magnesium oxide. (a) 40 nm commercial, $30 \text{ m}^2 \text{ g}^{-1}$; (b) 5 nm technical grade, $250 \text{ m}^2 \text{ g}^{-1}$; (c) 4 nm premium grade, $750 \text{ m}^2 \text{ g}^{-1}$; (d) normal, crystalline magnesium oxide (cubes) to nanoscale MgO. As crystal size changes, shape changes take place from cubes to hexagonal platelets, to intersecting wafflelike fiber. Images courtesy of Prof. Ken Klabunde, Chemistry Department, Kansas State University

These results, coupled with the recent findings in solgel, aerogel, and modified aerogel syntheses of porous metal oxides, as well as the literature of zeolites, pillared clays, and mesoporous silicas, suggest that future investigations will lead to precise control of pore sizes, pore size distribution, and chemical functionality of the pore walls.

The pores of friendly nanomaterials could be used to store strong acids, even super acids, in some cases. Likewise, weak bases or strong bases could be stored for use as needed in killing or destroying advanced enemy toxins. In addition, the nanomaterial itself could be produced with acidic sites (metal ions and/or certain proton donors) built into the pore walls and crystal faces. For example, titanium or zirconium ions can serve as acid sites if adjacent to sulfate species. Likewise, the proton forms of some transition-metal oxygen-anion clusters (polyoxometalates or “POMs”), like some metal oxides, are effective superacids in commercial processes. Polyoxometalates could be physically held within the pores or could be grafted onto the pore walls or onto the outer nanocrystal faces. Basic sites can also be built into the nanostructure, such as oxide anions near a metal cation vacancy. There are many other possibilities, such as sulfide substitution for oxide anions on the surface of the nanocrystals.

Storage of oxidizers in the pores should also be possible. The oxidizers could be incorporated as structural components of the material, physically entrapped, or immobilization by electrostatic and/or covalent bonds. POMs, in combination with friendly nanomaterials, present special promise, because POMs are versatile, reversible, and tunable oxidants and that, upon reduction by toxics, can be regenerated by air oxidation. Thus, nanomaterials will be accessible that catalyze the oxidative degradation of a range of threats and simultaneously exhibit complementary decontamination activities and other capabilities.

The opportunities for preparing a multipurpose catalytic material for decontamination, protection, and remediation of contaminated sites are very promising. Most CB agents are generally organic in structure, lessening the challenges associated with remediation of industrial recalcitrant compounds.

By combining catalytic sites with light absorption, photocatalysts are produced. By using nanostructures for these photocatalysts, several advantages are conveyed

on compounds that may otherwise be thermodynamically unstable in air. A range of engineered semiconducting metal oxides and POMs catalyze photochemical and electrochemical decontamination by providing new mechanisms to reach the thermodynamically more stable decontaminated forms via processes with lower activation energies, E_a . The use of photons and charge-transfer excited states, as in myriad TiO_2 - or POM-based light-driven decontamination processes, in general, can be obtained: (1) more active catalytic sites per unit mass or per unit volume; (2) more chromophores, or light-absorbing sites, per unit mass or unit volume; (3) nanocrystalline band gaps can be adjusted by size and by doping (additions of very small amounts of light absorbing atoms/molecules); (4) lifetimes of electron/hole pairs are sensitive to size and number of defect sites (electron or hole traps). Sometimes, this can be detrimental, but at other times, can be an advantage. For example, defects can serve as temporary traps for electrons and holes awaiting a second photon for further excitation, thus allowing more efficient use of relatively low energy visible light, instead of the higher energy but less abundant UV light.

Many nanostructural possibilities for creating very effective nanomaterials for photocatalytic decontamination are possible. The doping (or docking) of transition metal ions of visible light chromophores (e.g., vanadium, chromium, manganese, iron, or cobalt) into the backbone of nanostructured silica (SiO_2),¹⁵³ titania (TiO_2),¹⁵⁴ silica-titania,¹⁵⁵ as well as POMs,¹⁵⁶ has been demonstrated. Other possibilities, such as halogens, metal nanoparticles, or other POMs with particular tuned potentials could be stored in pores as special chromophores.

One notional solution would be a catalyst that is effective for decontamination of pollutants (including CB agents) at ambient temperatures in the dark, as well as in the light, that utilizes both visible and UV light. This would ensure that decontamination occurs at all times – at night, on cloudy days, on sunny days, whether inside or outside a building. A likely scenario for such a ubiquitous catalyst would entail a moderate capability using oxygen from air as the oxidant and a hydrolytic capability using water vapor in the air in the dark. Such a catalyst could achieve complete mineralization of the toxic threats in the presence of either sunlight or indoor visible light.

Other uses of nanostructured chromophores may include fluorescent nanoparticles or nanoparticle-based porous materials that change their light absorption or emission when a toxin is encountered. Some metal oxides and POMs already exhibit such properties. Likewise, electrochemical properties, including induced photocurrents, could be sensitive to encountering a toxin. Clearly, both decontamination and detection are relevant aspects here. Basic research is needed on the design and synthesis of engineered nanostructures whose electronic structures, thermal catalytic, photophysical (emission), and photocatalytic properties are strongly perturbed by the presence or absence of toxic compounds.

Malicious Design of Agents

A difficult challenge is to design a nanomaterial that can defeat encapsulated agents, involving trapping and coating the species, or trapping, stripping, and killing

a biological agent or rendering harmless a chemical agent. Malicious design of agents is widely expected to become increasingly sophisticated in delivery and stabilization methods. Many industrial and research compounds are commercially used to stabilize and transport chemicals. In the future, both CB agents may be encapsulated and time-released. Typical encapsulating materials are organic coatings, including sugars or other carbohydrate-based polymers, various polymers already in advanced development for drug encapsulation and controlled delivery, proteins, lipids, or hydrocarbons. Silica-based porous materials have been proposed in the inorganic sector.

Two approaches are considered for defeating such encapsulated agents. The first one might be called the “patient coat.” These would be functionalized nanomaterials that have adhesive properties so that the agent would adhere and thus would be trapped and in some instances coated rendering it inaccessible and consequently incapable of harming soldiers or equipment. In order to accomplish the design of such “patient coat” nanomaterials, fundamental adhesion studies of various materials to the coating materials mentioned above will be required.

In contrast to the “patient coat” concept, in some cases it will be desirable to totally destroy or kill the encapsulated agent. In this instance, oxidative and aggressive decontamination will be needed, for example, nano-oxides with adsorbed halogens, which are already known to be capable of coating, stripping, and killing bacterial spores.¹⁵⁷ Alternatively, work exploring nonhalogenated nano-oxides and POMs with effectively infinite shelf-lives could be engineered to be highly hydroscopic thus delivering water to the spores or an independent germinating agent. The resulting vegetative bacteria immediately destroyed by the intrinsic acid/base and/or oxidative properties of the nanomaterials.

Future developments could well include a combination of “patient coating” and “aggressive decontaminant,” where a nanomaterial produced adheres and degrades the encapsulating material and subsequently releases a decontaminating agent. Photodegradation is one methodology to accomplish neutralization of agents.

All-Purpose Decontamination

A longer term goal is to design nanomaterials that can select, detect, and decontaminate a wide range of agents. In the more distant future, time release and selective agents and decontaminants may do battle on the nanoscale. Hybrid materials combining organic and inorganic nanoparticles will be needed. Organic clathrates, binders, and basket-shaped molecules could be combined with inorganic oxides, POMs, metal organic frameworks, and chemically aggressive porous materials. Both organic pockets and inorganic pockets (sometimes referred to as baskets or pores) could be used to store reactive and biocidal materials used for decontamination. Ultimately, taggents will be attached that are optically sensitive so that immediate and remotely transmissible detection and differentiation of toxic materials (biological or chemical), encapsulated toxic materials, or destroyed toxin are possible.

Another consideration is, and will always be, to use nanostructures that themselves are not demonstrably harmful to humans or animals, and that, over time, degrade to benign moieties in the environment.

Indoor Decontamination

A major challenge to the current decontamination arsenal is the thorough decontamination of chemical or biological agents inside buildings or vehicles that cannot be summarily destroyed. Decontamination of the Hart office building in Washington, DC, is a prime example of this challenge. The use of highly toxic, highly corrosive gases to kill invasive bacteria, bacterial spores, or chemical agents will not be acceptable in the future. These corrosive, toxic gases destroy essentially everything in the interior of the building electronics (computers, sensors, switches) and fabrics (art, carpeting), rendering any contents useless and requiring eventual decontamination of the decontaminant. In addition, the decontaminating gas must be used in large volumes in order to fill the room with an appropriate concentration, and this large volume must be disposed of by venting to the atmosphere or trapping in some way.

First, nanomaterials must be designed and engineered with appropriate aerodynamic particle size and dispersion characteristics, which is certainly possible. A nanoparticle fog would be released into a contaminated room. If the aerodynamic particle size was appropriately small, probably less than $0.3\ \mu\text{m}$, it would completely disperse to all corners, crevices, and into carpets and tiles. Over time, perhaps several hours, the nanomaterial would aggregate, fall out, and be cleaned up using vacuum and filters. Indeed, this approach has already been demonstrated at the Midwest Research Institute (MRI) where a water-based aerosol of *Bacillus globiggi* spores (a nontoxic surrogate for anthrax spores) was dispersed into a room, and 5 min later, $\text{MgO}\cdot\text{Cl}_2$ nanopowders were dispersed. Over a several hour period, the air was sampled for spores, and in all cases, the spores did not vegetate and multiply under incubation. They were either completely dead or completely inactivated. Inactivation could result from initial direct bactericidal action of MgO nanoparticles on the spore and/or during germination which accompanies or immediately follows incubation.

This is a viable concept: that of defeating agents by passivation. Later, more vigorous treatment could actually kill a biological agent or neutralize completely a chemical agent. In other words, the nanopowders could be cleaned up and later treated in a well-equipped facility to completely render the contained agents harmless.

Thus, the advantages are (1) ease of clean-up of sorbed agent and passivated on the nanopowders; (2) the so collected nanopowders would contain important forensic evidence of the type of toxin used, whether chemical or biological; (3) minimal damage to the interior; and (4) enhanced safety in handling the powdery nanomaterial (as opposed to high pressure, toxic gases). Indeed, several promising nanomaterials (MgO , ZnO , TiO_2) have been shown to be safe for animals even after

extended inhalation and other exposures. Also, these nanopowders do not pass through typical gas masks because of their aggregated particulate nature.

In this area of interior decontamination, future nanomaterials hold great promise. Nonetheless, considerable research on environmentally safe nanomaterials with desired crystallite sizes, aerodynamic sizes, and decontamination characteristics is definitely needed.

Pre-exposure Protection and Decontamination

Multifunctional nanomaterials, such as organic–inorganic hybrids with surface sensors (chemical ligands that will bind selectively to selected agents) may also be built into personal protective gear. Optical or electronic signaling could identify the type of agent encountered and if the suit has been breached.

This protective suit technology could also use “smart” inorganic or organic membranes with gated porosity coupled with semipermeable membrane technology. Such membrane technology will require additional research and development; it will need to offer the following advantages: (1) ready permeability to air and water vapor; (2) size exclusion of bacteria and viruses while also incorporating decontamination capabilities; (3) embedded nanoparticles that sorb and decontaminate chemical agents (molecular vapors); and (4) size exclusion of droplets of water as well as more viscous chemical agents.

Coatings, such as protective paints, or temporary protective paints, or plastic coverings, will need to be developed. These coatings will be made up of advanced polymers which may depend on co-block or tri-block polymers with engineered hydrophobicity and hydrophilicity. Such coatings could contain hydrophobic or hydrophilic nanoscale pockets, baskets, or porous spheres that contain reactive organic functional groups for trapping and decontamination purposes. The desired porosity and reactivity properties, coupled with the necessary durability and flexibility, will need to be incorporated. These coatings will also need to support certain inorganic nanomaterials as additives for decontamination, and possibly optical or electronic signaling purposes.

Wide-Area Decontamination and Demilitarization

Nanomaterials for the purposes of passivating and destroying toxic agents that have been used in a battlefield situation or terrorist attack will likely be needed in the future. Requirements are low cost, ease of use, ease of delivery, ease of large-scale manufacture, and storability. Such nanomaterials need to be manufactured on a large enough scale that they can be stored in strategic locations across the country and in locations the military can gain access to quickly. They need to be safe to store and use, but once deployed, they need to act quickly and then degrade to

environmentally safe substances. Certain metal oxides and metal oxide–POM composites may meet these requirements, especially nanoscale magnesium oxide for sorption and hydrolytic properties, combined with environmentally safe POMs, to impart oxidative and catalytic properties. Sunlight active photocatalytic nanomaterials may be appropriate for some challenges for decontaminations of this type.

The agent may not need to be completely destroyed on site. In some instances, effective passivation may be appropriate and effective. This could be accomplished by developing a porous nanomaterial that causes the liquid agent to form a gel or a solid. Thus, a small amount of gelation agent or a nanocatalyst for polymerization could offer significant on site protection. Required decontamination and associated operations should entail minimum threat exposure and require minimal effort on the part of the warfighter. Ideally, only air or water as coreactants, and only small amounts of nanocatalyst or gelation agent, would be needed. In addition, the passivation should not develop much heat, so a modestly thermodynamically favorable process that occurs at room temperature would be best.

A possible approach would be dry powders of silica aerogels that contain within their pores free radical initiators. Another approach might be to use nanospheres of block copolymers that open up to imbibe the chemical agent. Biohazards in storage may also be encountered in a battlefield situation. Here, again, to attempt to completely destroy such stockpiles may not be defensible or appropriate. Application of a biocidal nanoparticle fog that coats all surfaces and crevices could be an effective short-term solution.¹⁵⁸ Any escaping organisms would be attacked and deactivated.

A Path Forward

It is also apparent that nanotechnology can and will be used in countermeasures against CB agents or today and emerging threats. To speed the gain of critical knowledge, research and development is needed in several areas, including, but not limited to, improved synthetic methods to produce (1) inorganic and organic nanomaterials; (2) multifunctional block and tri-block polymers; (3) multifunctional POMs; (4) hybrid (organic-inorganic) membranes; (5) nanomaterials with tunable and appropriate photochemical or electrochemical properties. Some essential components for advancement to desired 2030 state for decontamination are listed in Table 3.4.

Medical Countermeasures

Operational and timely medical countermeasures are primarily intended to prevent casualties of those exposed to threat agent. Major mission objectives also include preserving combat effectiveness and neutralizing enemy threats. Countermeasures

may be deployed for field diagnosis and treatments as well. Medical systems include all pharmaceuticals, biologics, and devices for these purposes.

The growth in nanotechnologies and its potential to aid in this mission is well recognized. The National Institutes of Health (NIH) has directed substantial funding to focus nanotechnology research to relevant areas of medical discovery. The NIH has initiated many nanomedicine research projects that are in progress and established medical nanotechnology research centers. Still in the early stages of the research plan, the NIH envisions nanomedicine proceeding from quantitative analysis of biomolecules and their communication pathways and developing new analyses tools and strategies, to manipulating living cells at the nanoscale to improve viability over the next 10 years.

The National Cancer Institute oversees a large R&D portfolio that further divides research directions. Within the NCI, research is roughly divided into areas of nanodevices and nanomaterials, nanotechnology-enabled therapeutics, diagnosis and biosensors, advanced imaging, and health and safety.

Formalized in the Cancer Nanotechnology Plan the envisioned outcome of the above research areas – having direct or indirect applications for CB defense – include the following:

- Early imaging agents and diagnostics that will allow clinicians to detect cancer in its earliest, most easily treatable, presymptomatic stage
- Systems that will provide real-time assessments of therapeutic and surgical efficacy for accelerating clinical translation
- Multifunctional, targeted devices capable of bypassing biological barriers to deliver multiple therapeutic agents at high local concentrations, with physiologically appropriate timing, directly to cancer cells and/or those tissues in the microenvironment that play a critical role in the growth and metastasis of cancer
- Agents capable of monitoring predictive molecular changes
- Surveillance systems that will detect mutations that may trigger the cancer process and genetic markers that indicate a predisposition for cancer
- Novel methods for managing the symptoms of cancer that adversely impact quality of life
- Research tools that will enable investigators to quickly identify new targets for clinical development and predict drug resistance

If sufficient researchers follow these recommended directions, a number of these capabilities will be demonstrated in the laboratory and investigational new drug applications will be filed over the next 3–5 years. Following this period, businesses would pursue new drug applications.

With the NIH's particular emphasis on detecting, preventing, and curing diseases common to the general populace, it is incumbent on the defense and security research communities to place their focus on the needs and hopes for nanotechnology to better protect against potential biological and chemical agents. In this sense, medical countermeasures refer to therapies that can provide medical protection for

individuals so that they preserve their combat strength, and provide medical management of casualties to enhance survivability, decrease convalescence time, and expedite return to duty.

By perusing the seven bulleted items above, one can envision scenarios where these technologies can be used to confound current medical countermeasures and produce a novel virulence that evades detection and medication. Current research funded by the DoD highlights several areas to support medical countermeasure research and includes immunization programs; development of antivirals, antibiotics, and toxin therapeutics; enhanced medical diagnostic capabilities including identification of specific types of species and toxins; and mechanistic studies to understand the toxicity of nontraditional agents with the goal of obtaining a license for use of prophylaxes, vaccines, and therapeutics in the 2020 timeframe.

Importantly, the Transformational Medical Technologies Initiative¹⁵⁹ aims to achieve the capability of rapid identification of genetically modified agents in the 2009-2013 timeframe. This wish list of understanding and capabilities provides a basis for evaluating potential capabilities of multifunctional and multitasking nanotechnologies that the defense and intelligence communities can exploit to better prepare individuals against advanced weaponry and weapons of mass destruction. Within the context of nanotechnologies that may be exploited for medical countermeasure development are carbon nanotubes, liposomes, gene transfections, quantum dots, TiO_2 , and a variety of other activated nanoparticles.¹⁶⁰

The demonstrated targeting specificity and uptake efficiency of ligand-directed nanoliposome complexes (EC1-3) make them effective delivery vehicles for use in rapid response medical countermeasures. The ability of this platform nanotechnology to swiftly deliver payloads such as gene medicines or small molecules specifically and efficiently to the target cells will result in a high, effective local concentration of the therapeutic agent and an immediate impact on the deleterious events. Moreover, the encapsulation of the therapeutics within the nanocomplexes serves to increase its stability in circulation, also enhancing efficacy. This modular nanotechnology can also be engineered to be multifunctional. Multiple therapeutic agents can be pooled and encapsulated as one payload, and multiple targeting ligands can be combined on the complex. Such strategies, targeting both the specific cell population and the detrimental intracellular process, would be effective against a wide variety of bioweapons such as nerve agents or viral/bacterial pathogens.

Countermeasures

On the basis of the possibilities for nanotechnology presented in the four future worlds, the following are some of the most important medical countermeasures:

- Convalescent sera (e.g., hyperimmunoglobulin) that can be rapidly scaled-up to meet immediate threats

Table 3.4 Essential components for advancement to desired 2030 state for decontamination

By 2010	By 2020	By 2030
Postexposure decontaminant - Materials with increased catalytic capability to make indigenous reagent decontamination (e.g., oxidative-reduction or photochemical reactions using mixed oxides, porphyrins, poly-oxometalates (POMs), or synthetic enzymes) - Rapid, contamination indicator, e.g., nanowires, transistors, with potential to transmit information	Postexposure decontaminant Enhanced selectivity such that decontaminant has various reactive sites to address multiple agents – chemical and biological	Postexposure decontaminant - Capable of decontaminating a broad-spectrum of agents - Operates autonomously (agent selective) - Threat agent detection systems that can detect novel chemical compounds or biological agents, e.g., based on functional groups and genetic signature
Decontaminating Precoat Surface coatings that encapsulate an agent and can be removed chemically or catalytically to be decontaminated at later stage	Decontaminating Precoat - Hybrid, multifunctional technology (e.g., merge of bio/nanotechnology) - Capable of achieving adaptability to various threats and technology - Molecular operational control (for example: electrochemical interface with multifunctional matrix)	Decontaminating Precoat Adaptive system (e.g., nano-biomimetic responsive)
Porous matrixes for reactive material - Controlled surfaces modification within the pore-enzymes, e.g., inorganic compounds, POMs - Electrochemical control to modify the reactions (e.g., using electrical current or protons)		- Autonomous recognition and response - Components capable of “communicating” to permit adaptability of the system (e.g., integrated communicative detection and reactivity systems)

(continued)

Table 3.4 (continued)

By 2010	By 2020	By 2030
	Large-scale decontamination/ demilitarization • Selective, but exceedingly efficient, decontaminants that render byproducts safe and are specific to the threat or agent (i.e., nanoscale oxides)	• Response to new or derivative agents of traditional chemical and biological agents
Large-scale decontamination/ demilitarization • Gellation materials • Nano catalysts to initiate polymerization		Large-scale decontamination/ demilitarization • Simple, deployable technologies for decontamination of large volumes of agent • Capability to deal with permissive and semipermissive access to agents and precursors

- Nanoadjuvants that increase countermeasure efficacy, both pre- and postexposure
- Systems biology approach to exploitation of adversarial technology
- Nanoparticle designed for CB adsorption

A number of scenarios in the Four Worlds of 2030 are shown in Fig. 3.14.

Science and Technology Capabilities Underlying the 2030 Nanoenabled Countermeasures

The science and technology capabilities that would be required to develop the countermeasures outlined above are presented below for the 2010 and 2020 timeframe.

During the decade from 2010 to 2020, distinct disciplines will continue to converge. Each will contribute unique perspective and technological expertise, resulting in a knowledge base and capabilities that are greater than the sum of the individual disciplines. Establishing active public and private partnerships is essential for acceleration of the development of the translational process, and interagency cooperation is crucial for success. Systems of nanocomponents can be envisioned

Dark Empires A multi-functional agent is released in the world of Dark Empires that evades traditional medical countermeasures. New countermeasures with polyclonal nanoparticles are needed, developed using a systems biology approach. Leveraging advanced systems biology enables the development of a practical tool for the rational design of nanoscale biostructures, which provide a means of rapidly fielding an effective nanotechnologically-based medical countermeasure for a particular threat agent or classes of agents.	Radical Game Changers A conventional strain of bacteria is apparently detected in healthy individuals across the US, aged 18 to 45. During medical treatment, antibiotics are found to be ineffective. After further inspection, the bacterium is found to be genetically-modified in the world of Radical Game Changers, requiring a novel treatment protocol. Breakthroughs in nanotechnology allow precise agent identification, proper focus of resources, and new treatment protocols.
Annoying States Defense efforts in the world of Annoying States develop enhanced bioscavenger therapeutics using nanoparticles for post-exposure prophylaxis. These nanoparticles are designed to selectively capture toxins or may serve as non-immunogenic transport vehicle adjuvants for bioscavenger technologies under development. When coupled to an appropriate detection technology, the threat is identified and these enhanced bioscavengers provide a means of rapid administration and increased effectiveness.	1,000 Points of Grayness A terrorist organization releases irritating nanoparticles with long-term carcinogenic effects at eight separate airports outside of the continental US. The initial dissemination is undetected. Passive networks of sensors at two U.S. points of entry, however, recognize an increase in the average elevated temperature of exposed passengers, and additional sensors show elevated levels of liver enzymes in airport waste streams. Mobile response laboratories, in coordination with National Guard Civil Support teams, are dispatched and intensive forensics reveal the commercial source of the nanoparticles. A legitimate commercial diagnostic contrast agent is soaked in a strong acid, treated with a weak basic solution, and subsequently dried to release the nanoparticles. In the world of 1000 Points of Grayness, technology developed in the United States may be co-opted for use in improvised attacks.

Fig. 3.14 Selected medical countermeasures scenarios

that are designed to self-assemble into multitasking nanodevices with complex biological capabilities. These specific multifunctional nanodevices can be designed to respond to various medical needs, including countermeasures against CB threats. To materialize this goal, a number of complementary mechanisms need to be in place. These include the capability to scale up production of these multifunctional nanomedicines and proper training of the first responders and other medical personnel to use these new medical countermeasures.

Design Challenges for 2010

Targeted delivery of nanoparticles to affected cells/tissues and selective coupling of target molecules to nanoparticles require the identification of specific intracellular pathways and the specific extracellular interactions between receptors and ligands. To enable deployment in the 2030 timeframe, receptor–ligand targets will need to be developed in the 2010 timeframe. Concurrent with this capability, knowledge of the basic properties describing the suitability of the nanomaterial as a drug will be required. These include understanding of the pharmacokinetics of the nanomaterials, their bioavailability, their toxicity, and immune system interactions. The physical

and chemical stability of the nanomaterials and their suspensions must be understood. Finally, their effectiveness, as well as the methods and ease of administration should be evaluated as well as interactions with other compounds. Some essential components for advancement to the desired 2030 state for medical countermeasures are listed in Table 3.5.

Design Challenges for 2020

In the 2020 timeframe, a protein/genomic library for select threat agents will be needed to rapidly design and develop therapeutic agents. Importantly, as diagnostic, therapeutic, and detection efforts by the US Defense and other research communities produce advanced technologies in the years leading to 2020, the CB protection community must maintain close coupling to these efforts, not only to synergize their knowledge base but to ensure that the most effective medical countermeasures exploit and are compatible with the best technologies available. Within this timeframe, selected nanomaterials should be in the proof-of-concept stage specifically for countering multiple CBRN agents. These candidate nanomaterials or nanomaterial systems must demonstrate, at least in principle, effective performance in ruggedized environments. To meet the 2030 deployment timeframe, scale-up issues must be addressed and should include information on manufacturing processes and feasibility and guidelines on the requirements for disposal characterization of the nanomaterials.

The nanotechnology capabilities identified for medical countermeasures revolve around developing suitable nanoparticles, or more generally, nanomaterials that expresses tailored multifunctionality, either for drug delivery or toxin adsorption. To develop such nanomaterials, a general path forward can be described. First, the target toxin, target organ and/or cell type must be identified. Next, sufficiently selective receptor–ligand pairs for the target must be identified. The nanocomplexes carrying their payloads must be designed and evaluated for *in vivo* efficacy. Then, the nanoenabled countermeasure must be demonstrated in the animal model and meet regulatory approval for use.

To further describe how the desired capabilities may be achieved, the following example is presented for developing a therapy for hemorrhagic fever, such as caused by the Ebola filovirus. First, existing research is evaluated, including basic knowledge of the particular virus and gene sequences. Other necessary basic information such as how the virus interacts with cells may or may not be known. Expanding this knowledge base may identify improved methods of countering the virus. In this case, basic research has identified that the virus is taken up by macrophages (monocytes), and that monocytes overexpress various receptors. Therefore, a number of receptor–ligand candidates are available for drug targeting. Through experiment (but, eventually, assisted by systems biology) siRNA is found to inhibit the virus. In the case of hemorrhagic fever, a number of different subtypes provide further complexity, and specific conserved viral sequences shared within a specific

subtype have been identified. Different siRNAs targeting each of these subtype sequences can be combined to achieve synergism.

The next step is identifying a suitable transport vector for the siRNA and evaluating candidate nanomaterials for drug transport *in vitro* and *in vivo*. Ultimately, to counter the fever in a person who is exposed or showing symptoms, a cocktail of siRNAs encapsulated in the ligand-targeted nanovehicle is administered. With further trials, dose–response curves and infusion protocols can be used to determine the commercial relevance of the technology.

Second example involves neurotropic nanovehicles to deliver therapeutics into specific neurons as medical countermeasures to the acute and chronic effect of nerve agents. The lack of effective counter measures for the horrific debilitating effects of nerve agents is an unmet medical need. The rapid action of a comprehensive remedy requires in-time, targeted, and efficient delivery of pathway- and target-specific therapeutics. An animal model of epilepsy, mimicking chemical nerve agent exposure, can be used to assess the potential of several nanomedicines to restore acetylcholinesterase functions, block acetylcholine receptors, and halt neurodegeneration. Owing to the modular nature of nanovehicles, neurotropic ligands targeting specific populations of neurons, in addition to a ligand that facilitates crossing the blood–brain barrier, can both be incorporated into the same nanovehicle. Here also the strategy is combinatorial, envisioning administration of multiple nanomedicines simultaneously for maximum effect.

In some threats, the body's immune response can be overly stimulated, as was the case during the 1918 influenza pandemic. The body can be devastated by the immune response, for example, by a flood of tissue necrosis factor or excessive populations of immune cells that cause tissue destruction. To counter this, nanoengineered bioscavengers may be designed to adsorb the blood-borne toxins and deactivate them or reduce their body burden by enhancing their natural excretion or filtering the nanomaterial–toxin complex from the blood.

In many instances, early drug development is the property of small companies with limited R&D budgets. Collaborations with large pharmaceutical companies likely will be required to bring candidate nanoenabled drugs through the US Food and Drug Administration (FDA) approval process.

Technical Challenges

Progress in developing nanotechnologies relies strongly on the complex integration of multidisciplinary teams of basic, applied, and clinical scientists and a keen understanding of business and regulatory processes. To realize the development and deployment of innovative medical countermeasures, several complementary enabling infrastructures and issues must be addressed. These are provided here in no particular order.

- Advanced, rapid diagnostics that identify a specific threat agent. Such basic information is required for effective prevention, detection, clinical diagnosis,

Table 3.5 Essential components for advancement to desired 2030 state for medical countermeasures

By 2010	By 2020	By 2030
Nano-based diagnostics • Ability to use nanoparticles in an “exploitation lab” to examine a threat agent and understand medical threat mechanisms. • Ability to identify an agent, then use system biology computation to reconstruct the antigen, understand its function, and develop a counter agent. (Assumes the antigen target is known, or that the precursor or agent is in hand.)	Nano-based therapeutics • Ability to design nano-materials for ease of administration • Ability to design nanomaterials with known interactions with compounds • Available production and disposal of nanomaterials • Available nanoencapsulation for liposomes for delivery of contrast agent, small molecules, or antigen for vaccine • Available nanoscale absorbants • Available nanoscale particles for postexposure prophylaxis	Nano-based countermeasures • Able to scale-up production of nano-enabled, in vivo CBRN agents in ruggedized environments • Available combination therapies that can treat a threat while developing the ideal antibody
Basic science • Published nanoscale protein genomic threat libraries • Known specific toxicities of nano- and nano/bio-based materials • Known receptor and ligand interactions for a number of probable targets	Basic science • Understanding of nanoparticle toxicity pharmacokinetics, and immune system interactions • Coupled diagnostic, detection, and therapeutic efforts	

and therapy. Technologies that can provide partial information are needed immediately, and others that can provide a thorough evaluation are needed as soon as practical.

- A family of animal models that support the evaluation of nanomaterials. In order to obtain FDA approval, the animal models must be relevant to the human model. The animal models need to identify and verify nanomaterial fate, toxicity, pharmacokinetics, and immune response.
- An understanding of the clinical relevance of measured or analyzed markers to indicate the pathophysiology of an agent. We must understand any pathogen’s effect – whether traditional, engineered, nanoenabled – on molecular pathophysiology.
- Methods to improve the backbone of siRNA, as well as the stability in circulation and shelf-life of the nanocomplex. In general, the stability of many proteins

—engineered proteins, antibody, antibody fragments, and so on — has not been demonstrated for in-field use. Methods are needed to engineer biosubstances to survive outside the clinic.

Nontechnical Barriers

Addressing nontechnical issues may be critical to realizing the deployment of nanotechnology-based medical countermeasures. Of significance, because many basic discoveries spawn from smaller companies, a mechanism is needed to assist small businesses to survive and prosper in today's research culture. Although small business innovative research grants are available, they may not be the best avenue for success given the limited federal funding available to continue support for successful projects.

Regulatory aspects also bear consideration. An investigational new drug application (IND) must be filed with the FDA in order to begin performance of studies in human on drug efficacy. Currently, FDA does not license platform technologies, leading to another regulatory challenge for novel medical or diagnostic systems based on nanotechnology. Moreover, the large investment required to move drugs through the regulatory approval process requires involvement of big pharmaceutical companies. Development of new drugs requires a long-term funding commitment and a realistic and predictable market. It is unclear how the defense community can marshal these forces given the high risk and dubious payoff for such technologies.

The multidisciplinary nature of innovative nanoscience research will involve many areas of expertise working together to realize breakthroughs. When a typical project requires the meaningful participation of a number of experts, budget requirements are expected to be higher than for single investigator working on an investigation into a more traditional area. Funding agencies must accept these justified budget increases to realize the aggressive goals needed for CB defense.

To better advance technologies that meet practical, in-field deployment requirements, a mechanism is needed to monitor progress of technology development compared to such that it continues in line with reality and with milestones. Moreover, there should be a mechanism by which companies are encouraged to participate in the research in the early stages to help maintain the focus on the end-point and the needs of the end user.

From Capability Needs to Research Priorities

The potential nanotechnology applications for CB defense described in this chapter are many and varied. Prioritization is needed of all of the possible research directions that the scientific and research community can take in order to achieve the most important goals outlined above. The eight research directions listed here have been identified for priority attention toward this end. More detailed research needs in each area are described in Chapter 5.

- Structure and function
- Bridging the bio–nano interface
- Self-assembly
- Power and energy
- Translational research
- System integration and engineering
- Modeling and simulation
- Systems biology

Notes and References

1. Schmedake TA, Cunin F, Link JR, Sailor MJ et al. (2002) Standoff detection of chemicals using porous silicon “smart dust” particles. *Adv. Mater.* 14: 1270–1272
2. Bruchez M, Moronne M, Gin P, Weiss S, Alivisatos AP et al. (1998) Semiconductor nanocrystals as fluorescent biological labels. *Science*. 281: 2013–2016
3. Chan WCW, Niw S. (1998) Quantum dot bio-conjugates for ultrasensitive non-isotopic detection. *Science*. 281: 2016–2018
4. Nam JM, Thaxton CS, Mirkin CA et al. (2003). Nanoparticle-based bio-bar codes for the ultrasensitive detection of proteins. *Science*. 301: 1884–1886
5. Alivisatos AP (2004) The use of nanocrystals in biological detection. *Nat. Biotech.* 22: 47–52
6. (2008) Chem. and biological defense program annual report to Congress. US Department of Defense. <http://www.acq.osd.mil/cp/cbdreports/cbdreporttocongress2008.pdf>
7. Bernard R. Information paper mission oriented protective posture (MOPP) and chem. protection. US Department of Defense. <http://www.gulfink.osd.mil/mopp/>
8. Joint service lightweight integrated suit technology (JSLIST) ensemble. http://www.jpeocbd.osd.mil/page_manager.asp?pg=2&sub=41
9. Schneider BR (2004) Combat effectiveness in MOPP-4 lessons from the U.S. Army CANE exercises, in *The War Next Time: Countering Rogue States and Terrorists Armed with Chem. and Biological Weapons*, 2nd edn, Schneider BR, Colonel Davis JA (eds). Air War College, Maxwell AFB, Alabama, pp 173–182. http://www.au.af.mil/au/awcgate/cpc-pubs/war_next_time/schneider2.pdf
10. Watanabe H, Vendamme R, Kunitake T. (2007) Development of fabrication of giant nanomembranes. *Bull. Chem. Soc. Jpn.* 80: 433–440.
11. Deval J, Umali TA, Spencer BL, Lan EH, Dunn B, Ho CM (2003) Reconfigurable hydrophobic/hydrophilic surfaces based on self-assembled monolayers. *Proc. Mater. Res. Soc.* 774: 203–208.
12. Rowsell J, Yaghi OM (2004) Metal-organic frameworks: A new class of porous mater. *Micro. Meso. Mater.* 73: 3.
13. Ni Z, Yasser A, Antoun T, Yaghi OMJ (2005) Porous metal-organic truncated octahedron constructed from paddle-wheel squares and terthiophene links. *Am. Chem. Soc.* 127: 12752.
14. NSA “Trusted Access Program Office.” <http://www.nsa.gov/business/tapo.cfm>
15. IA in action. (2006) Military information technology, Vol. 10. <http://www.military-information-technology.com/article.cfm?DocID=1298>
16. For more information, see Rodgers JR, Cebon D (eds.) (2006) *Mater. Inform. Mater. Res. Soc.* 31 http://www.mrs.org/s_mrs/sec_subscribe.asp?CID=7324&DID=181667
17. One early research example is Tsujita Y, Yoshimizu H, Okamoto S et al. (2005) Smart membrane: Preparation of molecular cavity and preferential sorption of small molecule. *J. Mol. Struct.* 739: 3–12.

18. Ouyang H, Archer M, Fauchet PM (2007) Porous silicon electrical and optical biosensors, in *Frontiers in Surface Nanophotonics*, in *Frontiers in Surface Nanophotonics*, Andrews DL and Gaburro Z (eds) pp. 49–72. Springer Berlin Heidelberg.
19. Kim HK, Min J, Kim JH, Chang H et al. (2006) Membrane electrode assembly for passive direct methanol fuel cells. *J. Power Sources*. 162: 497–501.
20. DeLuca NW, Elabd YA (2006) Polymer electrolyte membranes for the direct methanol fuel cell: A review. *J. Polym. Sci. B: Polym. Phys.* 44: 2201–2225.
21. Michel M, Taylor A, Sekol R, Podsiadlo P, Ho P, Kotov N, Thompson L, et al. (2007) High-performance nanostructured membrane electrode assemblies for fuel cells made by layer-by-layer assembly of carbon nanocolloids. *Adv. Mater.* 19: 3859–3864.
22. Fernández JE (2007) Materials for aesthetic, energy-efficient, and self-diagnostic buildings. *Science*. 315: 1807–1810.
23. Jung YC, Bhushan B (2006) Micro- and nanoscale characterization of hydrophobic and hydrophilic leaf surfaces. *Nanotechnology*. 17: 2758–2772.
24. Nosonovsky M, Bhushan B (2005) Roughness optimization for biomimetic superhydrophobic surfaces. *Microsyst. Technol.* 11: 535–549.
25. Palermo V, Samorì P Molecular self-assembly across multiple length scales. *Angew. Chem. Int. Ed.* 46: 4428–4432.
26. Cerulli M (2007) Chemical and biological threat detection systems of the future. *Chem-Bio Defense Q.* 4:18–21. http://www.jpeocbd.osd.mil/documents/Vol_4_Issue_2.pdf
27. Improving civilian medical response report. National Research Council. http://www.nap.edu/catalog.php?record_id=6364
28. Voiculescu I et al. (2006) Micropreconcentrator for enhanced trace detection of explosives and Chemical agents. *IEEE S. J.* 6: 1094–1104.
29. Hahn J, Lieber CM (2004) Direct ultrasensitive electrical detection of DNA and DNA sequence variations using nanowire nanosensors. *Nano Letters*, 4: 51–54.
30. McAlpine MC, Ahmad H, Wang D, Heath JR et al. (2007) Highly Ordered Nanowire arrays on plastic substrates for ultrasensitive flexible chemical sensors. *Nat. Mater.* 6: 379–384.
31. Standoff detection report: Existing and potential standoff explosive detection techniques. National Research Council. http://books.nap.edu/openbook.php?record_id=10998
32. Ward DR, Grady NK, Levin CS, Hals NJ, Wu Y, Nordlander P, Natelson D (2007) Electromigrated nanoscale gaps for surface-enhanced Raman spectroscopy. *Nano. Lett.* 7: 1396–1400.
33. Knap W, Lusakowski J, Teppe F, Dyakonova N, El Fatimy A et al. (2006) Terahertz emission and detection by plasma waves in nanometer size field effect transistors. *IEEE Trans. Electron.* E89C: 926–930.
34. Teppe F et al. (2006) Room temperature tunable detection of subterahertz radiation by plasma waves in nanometer In GaAs transistors. *Appl. Phys. Lett.* 89:222109–222123.
35. Lu JY et al. (2006) Terahertz microchip for illicit drug detection. *IEEE Photo. Tech. Lett.* 18: 2254–2256.
36. ChemSentry™ 150C point chemical vapor detection system. BAE Systems. http://www.ids.na.baesystems.com/Products/chemistry/chemsentry_1.htm.
37. Unattended ground sensors. (2004) Army Magazine. <http://www.ausa.org/webpub/DeptArmyMagazine.nsf/byid/CCRN-6CCSE7>.
38. McAlpine MC, Ahmad H, Wang D, Heath JR. (2007) Highly ordered nanowire arrays on plastic substrates for ultrasensitive flexible chemical sensors. *Nat Mater.* 6:379–384.
39. Braun E et al. (1998) DNA-templated assembly and electrode attachment of a conducting silver wire. *Nature*. 391: 775–778.
40. Fischler M et al. (2007) Formation of bimetallic Ag-Au nanowires by metallization of artificial DNA duplexes. *Small*. 3(6): 1049–1055.
41. Aherne D et al. (2007) Diameter-dependent evolution of failure current density of highly conducting DNA-templated gold nanowires. *Nanotechnology*. 18: 125205–125210.
42. Park SY, Lytton-Jean AKR, Lee B, Weigand S, Schatz GC, Mirkin CA et al. (2008) DNA-programmable nanoparticle crystallization. *Nature*. 451: 553–556.

43. Budimir N, Weston DJ, Creaser CS et al. (2007) Analysis of pharmaceutical formulations using atmospheric pressure ion mobility spectrometry combined with liquid chromatography and nano-electrospray ionization. *Analyst*. 132: 34–40.
44. Chang HW, Shih JS (2007) Surface acoustic wave immunosensors based on immobilized C60-proteins. *Sens. Actuators B Chem.* 121: 522–529.
45. Yoo BK, Park YW, Kang CY, Yoon SJ, Kim JS et al. (2006) Surface acoustic wave sensors to detect volatile gases by measuring output phase shift. *J. Electrocer.* 17: 1013–1017.
46. Rao YL, Zhang GG. (2006) Enhancing the sensitivity of SAW sensors with nanostructures. *Curr. NanoSci.* 2: 311–318.
47. Pinnaduwa LA et al. (2004) A sensitive, handheld vapor sensor based on microcantilevers. *Rev. Sci. Instrum.* 75: 4554–4557.
48. Novak JP et al. (2003) Nerve agent detection using networks of single-walled carbon nanotubes. *Appl. Phys. Lett.* 83: 4026–4028.
49. McGill RA et al. (2000) The “NRL-SAWRHINO”: A nose for toxic gases. *Sens. Actuators B Chem.* 65: 10–13.
50. Riegner et al. (1997) Qualitative evaluation of field ion spectrometry for chem. warfare agent detection. Proceedings of the 45th ASMS Conference on Mass Spectrometry and Allied Topics 473.
51. Sheehan PE, Whitman LJ (2005) Detection limits for nanoscale biosensors. *Nano. Lett.* 5: 803–807.
52. Rife JC et al. (2003) Design and performance of GMR sensors for the detection of magnetic microbeads in biosensors. *Sens. Actuators A Phys.* 107: 209–218.
53. Derks RJS, Dietzel A, Wimberger-Friedl R, Prins MWJ et al. (2007) Magnetic bead manipulation in a sub-microliter fluid volume applicable for biosensing. *Micro. Nano.* 3: 141–149.
54. Zhang DH et al. (2004) Detection of NO₂ down to ppb levels using individual and multiple In₂O₃ nanowire devices. *Nano. Lett.* 4: 1919–1924.
55. Blank K et al. (2003) A force-based protein biochip. *Proc. Natl. Acad. Sci. USA.* 100: 1356–1360.
56. Adams JD et al. (2005) Piezoelectric self-sensing of adsorption-induced microcantilever bending. *Sens. Actuators A Phys.* 121: 457–461.
57. Pinnaduwa LA, Ji HF, Thundat T et al. (2005) Moore’s law in homeland defense: An integrated sensor platform based on silicon microcantilevers. *IEEE Sens. J.* 5: 774–785.
58. Mack NH et al. (2007) Optical transduction of chemical forces. *Nano. Lett.* 7: 733–737.
59. Gao L, Song QY, Patterson GE, Cooks RG, Ouyang Z et al. (2006) Handheld rectilinear ion trap mass spectrometer. *Anal. Chem.* 78: 5994–6002.
60. Rugar D, Budakian R, Mamin HJ, Chui BW et al. (2004) Single spin detection by magnetic resonance force microscopy. *Nature.* 430: 329–332.
61. Mamin HJ, Budakian R, Chui BW, Rugar D et al. (2005) Magnetic resonance force microscopy of nuclear spins: Detection and manipulation of statistical polarization. *Phys. Rev. B* 72: 24,413–24,419.
62. Yan F, Vo-Dinh T. (2007) Surface-enhanced Raman scattering detection of chemical and biological agents using a portable Raman integrated tunable sensor. *Sens. Actuators B Chem.* 121: 61–66.
63. Mahajan S et al. (2007) Tuning plasmons on nano-structured substrates for NIR-SERS. *Phys. Chem. Chem. Phys.* 9: 104–109.
64. Okamoto T, H’Dhili F, Kawata S (2004) Towards plasmonic band gap laser. *Appl. Phys. Lett.* 85: 3968–3970.
65. Moskovits M, Jeong DH, Livneh T, Wu YY, Stucky GD (2006) Engineering nanostructures for single-molecule surface-enhanced Raman spectroscopy. *Isr. J. Chem.* 46: 283–291.
66. Su KH et al. (2006) Raman enhancement factor of a single tunable nanoplasmonic resonator. *J. Phys. Chem. B* 110: 3964–3968.
67. Stewart ME et al. (2006) Quantitative multispectral biosensing and 1D imaging using quasi-3D plasmonic crystals. *Proc. Natl. Acad. Sci. USA.* 103: 17143–17148.
68. Lim SH, Raorane D, Satyanarayana S, Majumdar A et al. (2006) Nano-chemo-mechanical sensor array platform for high-throughput Chem. analysis. *Sens. Actuators B Chem.* 1119: 466–474.

69. Reed J, Wilkinson P, Schmit J, Klug W, Gimzewski JK et al. (2006) Observation of nanoscale dynamics in cantilever sensor arrays. *Nanotechnology*. 17: 3873–3879.
70. Ancona MG, Snow AW, Foos EE, Kruppa W, Bass R et al. (2006) Scaling properties of gold nanocluster chemiresistor sensors. *IEEE Sens. J.* 6: 1403.
71. Lei H, Pitt WG (2007) Selection of polymeric sensor arrays for quantitative analysis. *Sen. Actuators B Chem.* 120: 386–391.
72. Shaffer RE, Rose-Pehrsson SL, McGill RA et al. (1999) A comparison study of chemical sensor array pattern recognition algorithms. *Anal. Chim. Act.* 384: 305–317.
73. Kramer KE, Rose-Pehrsson SL, Hammond MH, Tillett D, Streckert HH et al. (2007) Detection and classification of gaseous sulfur compounds by solid electrolyte cyclic voltammetry of cermet sensor array. *Anal. Chim. Act.* 584: 78–88.
74. Hammond MH et al. (2006) A novel chemical detector using cermet sensors and pattern recognition methods for toxic industrial chemicals. *Sens. Actuators B Chem.* 116: 135–144.
75. Porath D, Bezryadin A, De VS, Dekker C et al. (2000) Direct measurement of electrical transport through DNA molecules. *Nature*. 403: 635–638.
76. Kang SJ et al. (2007) High-performance electronics using dense, perfectly aligned arrays of single-walled carbon nanotubes. *Nat. Nanotech.* 2: 230–236.
77. Lay MD, Novak JP, Snow ES et al. (2004) Simple route to large-scale ordered arrays of liquid-deposited carbon nanotubes. *Nano. Lett.* 4: 603–606.
78. Dunwei Wang D, Sheriff BA, Heath JR (2006) Silicon p-FETs from ultrahigh density nanowire arrays. *Nano Lett.* 6: 1096–1100.
79. Patolsky F, Timko BP, Zheng G, Lieber CM et al. (2007) Nanowire-based devices in the life Sci.s. *MRS Bulletin* 32: 142–149.
80. Rhyner MN et al. (2006) Quantum dots and multifunctional nanoparticles: New contrast agents for tumor imaging. *Nanome.* 1: 209–217.
81. Alivisatos P. (2004) The use of nanocrystals in biological detection. *Nat. Biotechnol.* 22: 47–52.
82. Rhyner MN et al. (2006) Quantum dots and multifunctional nanoparticles: New contrast agents for tumor imaging. *Nanomedicine*. 1: 209–217.
83. Zimmer JP et al. (2006) Size series of small indium arsenide-zinc selenide core-shell nanocrystals and their application to in vivo imaging. *J. Am. Chem. Soc.* 128: 2526–2527.
84. Cheng MMC et al. (2006) Nanotechnologies for biomolecular detection and medical diagnostics. *Curr. Opin. Chem. Bio.* 10: 11–19.
85. Schmedake TA, Cunin F, Link JR, Sailor MJ. (2002) Standoff detection of chemicals using porous silicon “smart dust” particles.” *Adv. Mater.* 14: 1270–1272.
86. Salem MS, Sailor MJ, Harraz FA, Sakka T, Ogata YH (2006) Electrochemical stabilization of porous silicon multilayers for sensing various chemical compounds. *J. Appl. Phys.* 100: 083250–7.
87. Sboros V et al. (2006) Nanointerrogation of ultrasonic contrast agent microbubbles using atomic force microscopy. *Ultrasound Med. Biol.* 32: 579–588.
88. Martin CR (2006) Welcome to nanomedicine. *Nanomed.* 1: 5–9.
89. DeHennis AD, Wise KD (2005) A wireless microsystem for the remote sensing of pressure, temperature, and relative humidity. *J. Microelectromech. Sys.* 14: 12–22.
90. Lu CJ et al. (2005) First-generation hybrid MEMS gas chromatograph. *Lab on A Chip*. 5: 1123–1131.
91. Monaghan PB et al. (2007) Bead-based DNA diagnostic assay for chlamydia using nanoparticle-mediated surface-enhanced resonance Raman scattering detection within a lab-on-a-chip format. *Anal. Chem.* 79: 2844–2849.
92. Ligler FS et al. (2007) The array biosensor: Portable, automated systems. *Anal. Sci.* 23: 5–10.
93. Walt DR (2006) Fiber optic array biosensors. *Biotechnology*. 41: 529–535.
94. Zimmermann M, Delamarche E, Wolf M, Hunziker P et al. (2005) Biomed. *Microdevices*. 7(2): 99–110.
95. Lee YH, Yoo JM, Lee JH, Ju BK et al. (2006) All-carbon nanotube-based junction with virtual source and drain of carbon nanotubes by in situ one-step process for practical integrated nanoelectronics. *Appl. Phys. Lett.* 89: 243104–243107.
96. Choi WB, Kim DH, Choi YC, Huang JY et al. (2007) Junction single-wall carbon nanotube electronics. *JOM* 59: 44–49.

97. Bandaru PR (2007) Electrical characterization of carbon nanotube Y-junctions: A foundation for new nanoelectronics. *J. Mater. Sci.* 42: 1809–1818.
98. Avouris P, Chen J (2006) Nanotube electronics and optoelectronics. *Mater. Today*. 9: 46–54.
99. Schmidt M, Eich M, Huebner U, Boucher R et al. (2005) Electro-optically tunable photonic crystals. *Appl. Phys. Lett.* 87: 121110–121119.
100. Seydack M (2005) Nanoparticle labels in immunosensing using optical detection methods. *Biosens. Bioelectron.* 20: 2454–2469.
101. Kawazoe T, Yatsui T, Ohtsu M et al. (2006) Nanophotonics using optical near fields. *J. Non-Cryst. Sol.* 352: 2492–2495.
102. Huang Y, Duan XF, Lieber CM et al. (2005) Nanowires for integrated multicolor nanophotonics. *Small*. 1: 142–147.
103. Zheludev NI (2006) Single nanoparticle as photonic switch and optical memory element. *J Optics A Pure Appl. Optics*. 8: S1–S8.
104. Guan MJ, Liao WH (2007) On the efficiencies of piezoelectric energy harvesting circuits towards storage device voltages. *Smart Mater. Struct.* 16: 498–505.
105. Wang S et al. (2007) Energy harvesting with piezoelectric drum transducer. *Appl. Phys. Lett.* 90: 113506–113516.
106. Wang XD, Song JH, Liu J, Wang ZL et al. (2007) Direct-current nanogenerator driven by ultrasonic waves. *Science*. 316: 102–105.
107. Pei Q, Pelrine R, Stanford S, Kornbluh R, Rosenthal M et al. (2003) Electroelastomer rolls and their application for biomimetic walking robots. *Syn. Met.* 135: 129–131.
108. Pelrine R, Kornbluh R, Kofod G et al. (2000) High-strain actuator material based on dielectric elastomers. *Adv. Mater.* 12: 1223–1225.
109. Nguyen HQ, Cha GY, Yu JB, Huh JS et al. (2006) Improvement in sensitivity and recovery of single-walled carbon nanotube-based gas sensors. *Rare Metal Mater. Eng.* 35: 188–189.
110. Cho WS et al. (2006) Patterned multiwall carbon nanotube films as Mater. of NO₂ gas sensors. *Sens. Actuators B Chem.* 119: 180–185.
111. Johnson ATC et al. (2006) DNA-decorated carbon nanotubes for Chem. sensing. *Physica Status Solidi B-Basic Solid State Phys.* 243: 3252–3256.
112. Wang RX, Zhang DJ, Zhang YM, Liu CB et al. (2006) Boron-doped carbon nanotubes serving as a novel chemical sensor for formaldehyde. *J. Phys. Chem. B* 110: 18267–18271.
113. Sun ZY et al. (2006) Synthesis of ZrO₂-carbon nanotube composites and their application as chemiluminescent sensor material for ethanol. *J. Phys. Chem. B* 110: 13410–13414.
114. Choi HN, Yoon SH, Lyu YK, Lee WY et al. (2007) Electrogenated chemiluminescence ethanol biosensor based on carbon nanotube-titania-nafion composite film. *Electroanalysis*. 19: 459–465.
115. Ferrer-Anglada N, Kaempgen M, Roth S et al. (2006) Transparent and flexible carbon nanotube/polypyrrole and carbon nanotube/polyaniline pH sensors. *Phys. Status Solid B-Basic Solid State Phys.* 243: 3519–3523.
116. Pumera M, Merkoci A, Alegret S et al. (2006) Carbon nanotube-epoxy composites for electrochemical sensing. *Sens. Actuators B Chem.* 113: 617–622.
117. Watts PCP, Lyth SM, Mendoza E, Silva SRP et al. (2006) Polymer supported carbon nanotube arrays for field emission and sensor devices. *Appl. Phys. Lett.* 89: 103113–103124.
118. Fujiwara M, Shiokawa K, Hayashi K, Morigaki K, Nakahara Y et al. (2007) Direct encapsulation of BSA and DNA into silica microcapsules (hollow spheres). *J. Biomed. Mater. Res. A* 81: 103–112.
119. Al-Jamal WT, Kostarelos K (2007) Construction of nanoscale multicompartment liposomes for combinatory drug delivery. *Int. J. Pharm.* 331: 182–185.
120. Gomez-Graete C, Tsapis N, Besnard M, Bochot A, Fattal E et al. (2007) Encapsulation of dexamethasone into biodegradable polymeric nanoparticles. *Int. J. Pharm.* 331: 153–159.
121. Cui Y, Wei Q, Park H, Lieber CM et al. (2001) Nanowire nanosensors for highly sensitive and selective detection of biological and chemical species. *Science*. 293: 1289–1292.
122. Mahar B, Laslau C, Yip R, Sun Y et al. (2007) Development of carbon nanotube-based sensors – A review. *IEEE Sens. J.* 7: 266–284.

123. Cheng MM et al. (2006) Nanotechnologies for biomolecular detection and medical diagnostics. *Curr. Opin. Chem. Biol.* 10: 11–19.
124. Lang HP, Hegner M, Meyer E, Gerber C et al. (2002) Nanomechanics from atomic resolution to molecular recognition based on atomic force microscopy technology. *Nanotechnology*. 13: R29–R36.
125. Snow ES, Perkins FK, Robinson JA et al. (2006) Chemical vapor detection using single-walled carbon nanotubes. *Chem. Soc. Rev.* 35: 790–798.
126. Nanotechnology innovation for chemical, biological, radiological, and explosive (CBRE): Detection and protection. 2002. Final workshop report. WTEC and the AVS Science and Technology Society.
127. Moulton SE, Minett A, Wallace GG et al. (2005) Carbon nanotube based electronic and electrochemical sensors. *Sens. Lett.* 3: 183–193.
128. Su KH et al. (2006) Raman enhancement factor of a single tunable nanoplasmonic resonator. *J. Phys. Chem. B* 110: 3964–3968.
129. Astilean S (2007) Noble-metal nanostructures for controlling surface plasmons and sensing molecules. *Radiat. Phys. Chem.* 76: 436–439.
130. Yan XD, Ji HF, Thundat T et al. (2006) Microcantilever (MCL) biosensing. *Curr. Anal. Chem.* 2: 297–307.
131. Craighead H (2006) Future lab-on-a-chip technologies for interrogating individual molecules. *Nature*. 442: 387–393.
132. Weibel DB, Whitesides GM (2006) Applications of microfluidics in Chemical Biology. *Curr. Opin. Chem. Biol.* 10: 584–591.
133. Whitesides GM (2006) The origins and the future of microfluidics. *Nature*. 442: 368–373.
134. Kobasa D et al. (2007) Aberrant innate immune response in lethal infection of macaques with the 1918 influenza virus. *Nature*. 445: 319–323.
135. Ringeisen BR, Ray R, Little B et al. (2007) A miniature microbial fuel cell operating with an aerobic anode chamber. *J. Power Sources*. 165: 591–597.
136. Biffinger JC, Pietron J, Ray R, Little B, Ringeisen BR (2007) A biofilm enhanced miniature microbial fuel cell using *Shewanella oneidensis* DSP10 and oxygen reduction cathodes. *Biosens. Bioelectron.* 22: 1672–1679.
137. Wang ZL (2007) Nanopiezotronics. *Adv. Mater.* 19: 889–892.
138. Rearden M, Janin M Nano risk framework. <http://www.nanoriskframework.com/page.cfm?tagID=1095>.
139. Ostraat ML, Swain KA, Krajewski JJ et al. (2006) *Nanoparticle occupational safety and health (NOSH) consortium*. 1–38 DuPont.
140. Mattis DC (2006) Magnetism and superconductivity in nanoarchitectures. *Phys. B Condens. Matter*. 384: 239–243.
141. Mulvaney SP, Mattoussi HM, Whitman LJ et al. (2004) Incorporating fluorescent dyes and quantum dots into magnetic microbeads for immunoassays. *Biotechnology*. 36: 602–609.
142. Choi Y, Baker LA, Hillebrenner H, Martin CR et al. (2006) Biosensing with conically shaped nanopores and nanotubes. *Phys. Chem. Chem. Phys.* 8: 4976–4988.
143. Silva GA (2007) Nanotech approaches for drug and small molecule delivery across the blood brain barrier. *Surg. Neurol.* 67: 113–116.
144. Gross PG, Kartalov EP, Scherer A, Weiner LP et al. (2007) Applications of microfluidics for neuronal studies. *J. Neurol. Sci.* 252: 135–143.
145. Lieber CM, Wang ZL (2007) Functional nanowires. *MRS Bull.* 32: 99–108.
146. Lucas P et al. (2006) Infrared biosensors using hydrophobic chalcogenide fibers sensitized with live cells. *Sens. Actuators B Chem.* 119: 355–362.
147. Gray SA et al. (2001) Design and demonstration of an automated cell-based biosensor. *Biosens. Bioelectron.* 16: 535–542.
148. Patolsky F et al. (2006) Detection, stimulation, and inhibition of neuronal signals with high-density nanowire transistor arrays. *Science*. 313: 1100–1104.

149. Khor IW, Lin T, Langedijk JP, Johnson JE, Manchester M et al. (2002) Novel strategy for inhibiting viral entry by use of a cellular receptor-plant virus chimera. *J. Virol.* 76(9): 4412–4419.
150. Myc A, Kukowska-Latallo JF, Bielinska AU, Cao P, Myc PP, Janczak K, Sturm TR, Grabinski MS, Landers JJ, Young KS, Chang J, Hamouda T, Olszewski MA, Baker JR (2003) Development of immune response that protects mice from viral pneumonitis after a single intranasal immunization with influenza A virus and nanoemulsion. *Vaccine.* 21: 3801–3809.
151. Hamouda T, Myc A, Donovan B, Shih AY, Reuter JD, Baker JR (2001) A novel surfactant nanoemulsion with a unique non-irritant topical antimicrobial activity against bacteria, enveloped viruses and fungi. *Microbiol. Res.* 156: 1–7.
152. Richards R, Li W, Decker S, Davidson C, Koper O, Zaikovski V, Volodin A, Rieker T, Klabunde KJ (2000) Consolidation of metal oxide nanocrystals. *Reactive pellets with controllable pore structure that represent a new family of porous, inorganic materials.* *J. Amer. Chem. Soc.* 122: 4921–4925.
153. Gilliot M et al. (2006) Optical properties of cobalt clusters implanted in thin silica layers. *Phys. Rev. B* 74: 454–465.
154. Pauporté T, Bedioui F, Lincot D et al. (2005) Nanostructured zinc oxide-chromophore hybrid films with multicolored electrochromic properties. *J. Mater. Chem.* 15: 1552–1559.
155. Suh WH, Jang AR, Suh Y-H, Suslick KS et al. Porous, hollow, and ball-in-ball metal oxide microspheres: Preparation, endocytosis, and cytotoxicity. *Adv. Mater.* 18: 1832–1837.
156. Kurth DG, Liu S, Volkmer D, et al. (2003) Polyoxometalates in tailored architectures: From structure to function, in Polyoxometalate Molecular Science, Borrás-Almenar JJ, Coronado E, Muller A, Pope MT (eds). Springer, New York.
157. Klabunde KJ, Mulukutla R (2001) Chemical and catalytic aspects of nanocrystals, in Nanoscale Materials in Chemistry, Klabunde KJ (ed), pp 223–261. Wiley InterScience, New York.
158. Koper O, Klabunde J, Marchin G, Klabunde KJ, Stoimenov P, Bohra L et al. (2002) Nanoscale powders and formulations with biocidal activity toward spores and vegetative cells of bacillus species, viruses, and toxins. *Curr. Microbiol.* 44: 49–55.
159. DoD Chemical and Biological Defense Program (CBDP) Transformational Medical technologies Initiative 2008 Report to Congress, <http://www.tmti-cbdefense.org/>.
160. National Research Council. (2004) Giving full measure to countermeasures: Addressing problems in the DoD program to develop medical countermeasures against biological warfare agents. Washington, DC: National Academies.
161. Park KS et al. (2006) Exceptional chemical and thermal stability of zeolitic imidazolate frameworks. *Proc. Natl. Acad. Sci. USA.* 103(27): 10186–10191.
162. McAlpine MC, Ahmad H, Wang D and Heath JR (2007) Highly ordered nanowire arrays on plastic substrates for ultrasensitive flexible chemical sensors. *Nat. Mater.* 6: 379–384.
163. Introduction to Nanotechnology, in Nanoscale Materials in Chemistry, Klabunde, KJ (ed). Wiley Interscience, New York (2001).

Chapter 4

Potential Malfeasant Cooption of Nanotechnology

Today, two emerging technologies, nanotechnology and biotechnology, have the power to alter our world, and warfare, even more fundamentally than information technology.

Most writers agree it will be 20 years or more before nanotech hits full stride....

Colonel T.X. Hammes. USMC (ret)¹

Among the highest priorities for the US and the Department of Defense in the twenty-first century is to deny the acquisition and use of weapons of mass destruction by hostile states, substate actors, or nonstate actors for use in acts against the US and its allies.² Anticipating the types of threats that may emerge as science and technology advance, the potential consequences of those threats, and the probability that enemies will obtain or pursue them is necessary for preparing for the future security of the nation and the wider world community. This is also a critical part of near-term defensive planning.

Nanotechnology is a prime example of this type of enabling and potentially game-changing technology. Today, almost all developed countries are vigorously pursuing nanotechnology developments with well-funded programs in the US, Japan, China, Russia, Israel, Taiwan, India, Iran, and across Europe. The global nature of this research means that much of the nanotechnology advancement recently achieved, and that projected for the future will likely be available to friends and adversaries.

The ubiquitous nature of nanotechnology and biotechnology means that their applications will be far reaching. Understanding potential proliferation challenges and threats that may be wielded through application of these technologies is critical. The development of countermeasures to those threats is a national concern, and a strong defensive capability is also important as a deterrent.

The scope and nature of future nanotechnology-based proliferation threats can be assessed across several broad categories:

- Novel nanotechnology-based biochemical weapons
- Nanoparticles and nanomaterials with toxicological or deleterious health properties
- Bio- and nanoenabled influence operations
- Nanotechnology-enabled evasion of medical countermeasures
- Self-assembled materials and devices, and the potential of molecular assemblers

Considerations of these threats from a technological and national security perspective include the limits to use, the overall national security consequences of the threat, and the potential impact of the threat on military operations. The science and technology capabilities necessary to realize nanotechnology-enabled threats in 2030 can be extrapolated from the current state of research and a determination of critical nodes required to achieve those possibilities. Preventing or inhibiting existing national and global research endeavors is a difficult if not impossible. For these reasons, it may be more useful to understand the intended applications as well as their potentially malicious uses to ensure development of appropriate countermeasures.

Novel Nanotechnology-Enabled Biochemical Weapons

Nanotechnology's primary role in transforming today's benign research advances into the future threats envisioned may be in providing structures at the molecular level that aid in the dissemination and stabilization of novel agents and the design of those agents to achieve the desired negative outcome.

Nanotechnology and biotechnology enjoy a great deal of overlap in many research laboratories. A current focus of research in this crosscutting area is on using genetically engineered viruses, proteins, DNA, and other biological moieties as templates to assemble nanostructures and to understand structure–function biological interactions.³ For example, by combining a genetically engineered protein with nanoscale particles, researchers have created a new kind of solar cell.⁴ The development of “artificial nanosystems with biomimetic functionality but without [biological] fragility” has been identified as a major long-term research goal.⁵

Advances in the life sciences and nanotechnology are occurring rapidly, making it possible to interface easily to and enhance living systems in a variety of ways. Approaches currently being explored include controlled and sustainable drug delivery using nanoshells, nanotubes, nanocrystals, and dendrimers; multifunctional nanoparticles that combine targeting agents with therapeutic agents; nanoparticles that can be targeted and assembled *in vivo* using drug-like subunits; and nanoparticles that can be triggered by external sources. Nano- and microencapsulation technologies are rapidly multiplying and diversifying, owing in large measure to research in the pharmaceutical and biotechnology industries. The agricultural, food processing, and chemical industries also promote this trend.

These potential synergies between biotechnology and nanotechnology show not only tremendous promise but also raise new concerns. Much has been accomplished in nanotechnology research, for example, that parallels biotechnology and raises concerns similar to those associated with genetic engineering and genetically modified organisms. It is unclear, however, why the potential for unintended consequences from nanobiotechnology discoveries have not received similar attention. The potential, for example, for nanotechnology to affect or enhance the virulence, resistance, transmissibility, latency, stability, or dispersal characteristics of biological agents

appears to be of little concern. Encapsulation technologies, for example, are currently not subject to export controls or international arms control regimes.

A commonly conjectured threat scenario involves conventional agents packaged in nanomaterials. For instance, inhalable nanoparticles may be developed as a threat agent or threat agent carrier. It should be noted that most conventional threats, however, commonly operate via the inhalation pathway, so conventional protection methods apply. The primary therapy for a nanoenabled threat agent may be identical to current or developing therapies against that unenhanced threat agent. There may not be a distinction in treating Ebola virus carried by a nanomaterial versus one introduced by normal modes of transmission. A nanomaterial, however, may enhance the stability of a threat agent to facilitate weaponization, improve delivery efficacy, or modify the pathway of infection. For example, a nanomaterial may be used to target the agent to different organ pathways than normally targeted, causing the disease to present itself in novel ways.

The highest priority future threat among the nanotechnology-enabled biochemical weapons, as identified by the participants at the NanoCBD2030 Workshop, was the aerosol delivery of nanoparticles that contain proteins, peptides, prions, RNA, or DNA. This notional threat arises from the potential cooption of the use of nanoparticles to deliver therapeutic agents to cells; delivery of genetic material, proteins, and peptides to cells presents tremendous opportunities for future therapeutic treatments and vaccines.⁶ Given the wide range of different pharmaceutical or chemotherapeutic payloads and the many types of tissues and cells that need to be targeted for a variety of functions, a number of delivery methodologies and nanomaterials are under investigation.⁷

This broad nature of this research provides a large knowledge base and a vast number of approaches that could be used for the development of novel nanotechnology-based weapons. Some aspects of the weapon development would have to be further refined, and additional research may be required depending on the mode of delivery. For example, the effectiveness and stability of an aerosolized particle might not be found in the published literature if the drug were developed as an oral or injectable substance.

If a nanotechnology-based weapon is delivered through the air, the nanoparticles would have the ability to affect specific tissues or cells and release toxins to lung cells, brain cells, or blood cells that could deliver the molecules throughout the body. The resulting modulation of genetic material or release of toxins into the blood stream or the brain could cause illness or death. The most imminent threat appears to be aerosol delivery due to its ability to infect large numbers of individuals. A number of scenarios are outlined below. Alternative modes of delivery include delivery through food, water, or surface contact.

Several classes of nanomaterials, including carbon nanotubes (CNTs), have the ability to translocate molecules, such as DNA⁸ and proteins,⁹ into the interior of cells. These CNTs have been functionalized giving them the required solubility and ability to deliver molecules across cell membranes. While the toxicity of CNTs in these applications is not well characterized, initial studies suggest that at low doses and at timescales of days, merely functionalized CNTs were not toxic to cells. Nanotubes have also been used as a delivery mechanism for protein and peptide

molecules.¹⁰ Single-walled carbon nanotubes (SWNTs) have been shown to deliver nonspecifically bound proteins, such as cytochrome *c* (cyt-*c*), to the cell while maintaining biological activity.¹¹ Apoptosis, or cellular death, was observed upon uptake of cyt-*c*, which would be the expected result since cyt-*c* induces apoptosis. Experiments are still required to demonstrate whether the cyt-*c* activity was active even after detaching from the SWNT or only while still bound. They also noted that the intracellular transportation by SWNTs worked for small- to medium-size proteins (molecular weight ≤ 80 kDa); however, transport of a larger protein, human immunoglobulin (molecular weight ≈ 150 kDa), was not as successful. CNTs may serve as a means to translocate proteins, such as the *Bacillus anthracis* lethal factor (LF) and edema factor (EF), thereby potentially creating a method to circumvent the current vaccine, which is based on the *B. anthracis* protective antigen (PA).

In a more futuristic scenario, prions or proteins with similar functions could be attached to nanoenabled aerosol particles that have the capability to cross the blood-brain barrier. Prions, or proteinaceous infectious particles, are thought to cause such diseases as bovine spongiform encephalopathy (BSE), commonly known as mad cow disease. BSE is a fatal neurodegenerative disease in cattle but is thought to be transmissible to humans and causes a variant of Creutzfeldt-Jakob disease. Creutzfeldt-Jakob disease is caused by a misfolded protein. The normal form of the protein is found in the brains of all mammals, and is harmless; however, the abnormal form converts other normally folded proteins into the altered conformation, thereby creating more prions. The presence of the misfolded protein causes loss of motor coordination, dementia, and death. There is a large amount of research underway related to nanoparticles crossing the blood-brain barrier to allow for drug delivery to the central nervous system (CNS),¹² including questions of resulting toxicity.¹³ Current technical prohibitions to realizing such a threat include (but are not limited to) developing a delivery mechanism for prions and determining the infectious dose and its time dependence.

All of the beneficial applications discussed present hypothetical scenarios in which the technology could be inverted for hostile applications. As with siRNA, delivery of DNA and oligonucleotides to cells *in vivo* has been problematic and nanotechnology offers potential solutions. Achievement of successful gene therapies is dependent on development vectors that allow for efficient and targeted delivery of genes to targeted cells or tissues with minimal toxicity.^{14,15} Current approaches utilize viral vectors as they allow for high transformation efficiencies and expression, but adverse effects elicited by the immune response to viral proteins, potential for replication, limited DNA transport ability, and cost have necessitated the need for alternative approaches.¹⁶ The difficulties of delivering DNA to cells *in vivo* has been a setback for gene therapy and led to development of nonviral DNA delivery vehicles.¹⁷ Development of an inhalable form of siRNA has been successful *in vitro* for treatment of lung cancer and inflammatory lung disease. Liquid-spray systems and more advanced dry powder systems are currently being developed in commercial and research laboratories, and both could potentially be used in the future.¹⁸

Magnetic nanoparticle-based gene delivery is also being investigated as a method for delivering genetic material *in vitro* and *in vivo*. Drugs and genetic material, including DNA and siRNA, have been attached to biocompatible particles and then focused to target sites using high-field gradient magnets. This approach provides a rapid and efficient transfection. This technique still requires more research before development as a therapeutic agent for several reasons, including the difficulty of capturing the particle complex using a magnet source that creates a high gradient. Currently, it is not feasible to capture particles more than a few centimeters deep, but work toward the delivery of drugs and genetic material is continuing. In 2030, development of magnets that create this type of mechanism will most likely be available and could lend itself to a type of triggerable weapon, whereby those infected and within the required distance of a hidden magnet would become ill.

There are a vast number of possibilities that can be imagined and must be considered by DoD to prepare for the future. Another area is nonviral delivery. As successes in nonviral delivery continue to increase, the possibility of creating a germ line modification to humans, plants, or animals also becomes a possibility. This would be permanent modification to the genome that would be passed on to future generations. These types of modifications could be debilitating genetic diseases that affect humans or animals, crops that no longer produce, and disruption of entire ecosystems.

A similar threat is the potential to develop a nanoscale agent targeting a specific ethnic or racial group. A nanoscale agent designed to target a particular phenotype could be widely deployed yet only affect a narrow population. Although this may be possible notionally, it is an extremely unlikely threat for a number of reasons, primarily because the genetic dissimilarities of subgroups across a single racial or ethnic group are frequently larger than intergroup differences.¹⁹ The chance that such a notional agent could target unintended victims is high.

Nanoparticles with Toxic or Deleterious Health Effects

In the national policy discussion of potential risks associated with nanotechnology, the discussion has been dominated by the possible health and environmental consequences associated with nanoengineered materials. A plethora of research has begun to explore the behavior of nanoengineered materials with physiological systems.²⁰ The National Nanotechnology Initiative has also recommended several technical research needs and priorities for environmental, health, and safety of nanotechnology.²¹

The highest priority threats in this area include nanoparticles capable of destroying brain tissue or cells through inhalation or ingestion in food or water supplies. Studies of air pollution, particulate matter, and nanoparticle toxicology have lead to the development of a framework related to the potential consequences of inhalation exposure of nanoparticles, including lung inflammation and cardiovascular injury

either through direct contact with the particles or through effects mediated by the CNS. Inhalation or ingestion of nanoparticles can cause blood vessel dysfunction and systemic inflammation that can also affect cardiovascular health²² or produce effects similar to asbestos exposure.²³

There are many uncertainties surrounding the environmental, health, and safety risks of nanomaterials and nanoparticles.²⁴ As more information becomes available, it is clear that some nanoparticles have toxic effects, both short- and long-term. Predictive models for health and safety considerations would allow wider use for many applications. Given the increased exposure and possible side effects from nanoparticles, many countries are performing research to better understand the interaction of nanoparticles and biological systems. It is established that these particles can enter the body through skin, lungs, and the intestinal tract and can have novel activities compared to bulk materials of the same composition.²⁵ Factors that are important for understanding the potential toxicity include size, shape, surface area, charge, and surface reactivity.

The potential consequences of inhalation exposure to nanoparticles are only beginning to be understood. The toxicology of metal fumes, radionuclides, nuisance dusts, rat lung overload, the toxicology of silica, asbestos, synthetic vitreous fibers, and pollution particles can all be used to gain insight into the behavior of nanoparticles. Currently, there is no model to predict the toxicity or safety of nanoparticles, and little information is available with regard to human exposure and risks related to levels and duration of exposure.

Utilizing current research and the expected future data related to nanoparticles, it is possible to envision a scenario where nanoparticles released in a building or delivered through food or water supplies would be lethal or cause illness. Some current challenges to this type of weaponization are the difficulties of large-scale production, safety considerations for the developers, and the mode of delivery. Given the predicted growth in nanotechnology by 2030, these challenges may lessen; toxic particles could be commercially available, creating a scenario where it is possible to buy such a weapon. Depending on the intent of individuals designing the notional weapon, it could be developed to cause immediate results or to have long-term effects that allow for widespread exposure as persons entering a contaminated area or building are exposed, but the cause is not be immediately apparent. One futuristic possibility is the development of nanoparticles devised to have coatings that allow them to contain and stabilize superacids, and once inhaled or ingested, the particle coatings are triggered or enable the release of the superacid into the body.

Several studies determined that inhaled or injected nanoparticles enter systemic circulation and can access various organs and tissues or they can enter the CNS via neuronal transport providing many opportunities to cause damage depending on the toxicity of the nanoparticle and the dose. Most nanoparticles at a high enough dose will induce significant pulmonary inflammatory responses and systemic effects. Studies performed in the early 1990s looked at the pulmonary inflammation and interstitial translocation of the same mass of fine and ultrafine TiO_2 (250 and 20 nm) and of Al_2O_3 particles (500 and 20 nm).²⁶ The authors concluded that ultrafine

particles (0.02–0.03 μm in diameter) infiltrate tissues better than fine particles (0.2–0.5 μm in diameter), causing increased pulmonary toxicity. This increase is related to ultrafine particles having a larger surface area for the same mass. TiO_2 particles have been used for revolutionary drug delivery and imaging applications.

Recent experiments have linked TiO_2 particles to possible damage to brain cells. Results obtained from rodents exposed to different sizes of TiO_2 particles showed negligible effects,²⁷ but many *in vitro* studies suggest that these nanoparticles induce oxidative stress in various cell types, from osteoblasts²⁸ to alveolar macrophages.²⁹ Oxidative stress can be induced by reactive oxygen species, and monitoring the chemical signature provides a methodology for nanotoxicity testing.³⁰ Knowing that nanoparticles can cross the blood-brain barrier and that the CNS is vulnerable to oxidative stress, the effect of TiO_2 nanoparticles in Degussa's Aeroxide P25 was tested with cultured microglia cells.³¹ Microglia cells respond to exogenous stimuli and generate an "oxidative burst" in order to destroy the potentially damaging stimuli. This burst releases superoxide anions including hydrogen peroxide and hydroxyl radicals. If a prolonged release occurred, this effect could damage the brain. This type of biochemical activity has been implicated as the cause of neuronal damage in neurodegenerative diseases. The results obtained from measuring the ROS activity of microglia cells exposed to P25 indicate that there was prolonged release of ROS. The next experiments will determine if the release actually caused neuronal damage.³² For 2030, encapsulated TiO_2 could be developed as a targeted weapon to cause oxidative damaging.

Another potential threat scenario is the delivery of seemingly benign nanomaterial threat agents that become toxic upon activation from external sources. For instance, nanoparticles have been designed for activation by near-infrared photons. The activated nanoparticles can be toxic. Others are activated by mild X-ray radiation. Such nanoenabled threat agents present difficulty in designing an effective countermeasure. Once nanoparticles deposit in the target tissue, little can be done to eliminate them or their function. One possibility is a nanomaterial capable of targeting the threat nanoparticle and changing the chemistry of the threat nanoparticle to reduce or eliminate its ability to activate, for example, by oxidizing the material.

A related threat is the potential to introduce nanoparticles into the human body or brain without the subject's knowledge. These may remain dormant for hours, or years, until activated by an external electromagnetic source. The particles could then destroy tissue or have other deleterious effects.

Bio- and Nanoenabled Influence Operations

One potential malicious application of nanotechnology is in influence operations, or activities with indirect effects that interfere with an adversary's chemical or biological weapons production.³³ Traditionally, influence operations (sometimes called information operations - IO) are a form of cyber warfare designed to influence the information technology of an adversary. In a similar manner, chemical and biologi-

cal weapons can be used as a tactical disruption or malicious influence against biological systems. As with cyber-IO, bio-IO threats may combine multiple modes of operation that are individually of low fidelity but produce a high fidelity result.

Bio-IO threats can be used against agricultural, bacterial, or human systems both to prevent spread of disease and to annihilate a threat. As part of a fielded sensor or diagnostic system, a nanoenabled bio-IO weapon could exploit indigenous agricultural or bacterial systems as a means for surveillance, making use of plant, insect, or animal sentinels as part of a larger sensor network. The sensor network may also include nanoenabled motes or advanced nanosatellites³⁴ and leverage handheld personal devices such as cell phones, iPods, or PDAs. Nanoenabled bio-IO could also moderate attacks via medical implants that provide real-time molecular imaging and reporting of disrupted biological processes.

More revolutionary approaches may incorporate synthetic biology to redesign or reprogram cells, organisms, or signaling pathways. This can be done as a preventative measure, or in real time as a means for a tactical disruption of biological circuitry to interrupt deleterious physiological responses, such as the shock effects associated with *B. anthracis* or the effects on the nervous system of Botulinum toxin.

Nanotechnology-Enabled Evasion of Medical Countermeasures

Nanoenabled materials and technologies may also be used to evade traditional medical countermeasures. Vaccines, antivirals, and antibiotics are the current first defense against many biological weapons. Nanotechnology may be used for this application in two different ways: First, nanotechnology can be an enabling tool to develop a weapon that would not be affected by a known countermeasure. Second, like biotechnological immune modulators, nanotechnology could be used to disrupt the immune system, through either suppression or overstimulation, and prevent it from functioning. Such a notional weapon developed to disrupt the entire immune system would not require knowledge of what countermeasures are in place.

An example that would fall into the first category is a simple methodology that could be used to overcome the currently available vaccine for *B. anthracis*, or anthrax. The anthrax toxin is composed of three proteins: edema factor (EF), lethal factor (LF), and the protective antigen (PA). The portion responsible for binding the cell surface is PA, which enables to enter the cell via endocytosis, where they exert their toxic effects. EF is an adenylate cyclase, and LF is a protease that affects certain kinases and thereby kills macrophage cells. If PA is not active or present, then EF and LF cannot enter the cell thereby creating an ineffective toxin.^{35–38} Because LF and EF are proteins, conjugation to a nanotube, either single-walled or multi-walled carbon nanotube, could be used to enable transport across the cell membrane. In such a scenario, while PA is not present, the vaccine would be ineffective, and illness or death from the LF and EF inside the cell would result. The dose required for such a weapon would likely be significantly higher than with the natural bacteria (BA) as there is not a pathway for replication of EF and LF.

An approach in the second category would be to utilize current immunological research to identify particular cascade events or pathways in the immune system. By blocking or overstimulating immune system pathways, not only are our countermeasures defeated but novel agents can be created. In addition, these agents could be very fast-acting, preventing treatment options from being effective. In a phase I trial of the anti-CD28 monoclonal antibody TGN1412,³⁹ an antibody developed for the potential treatment of autoimmune diseases such as multiple sclerosis, the antibody was intended to gently stimulate the immune system, but instead it led to multiple organ failure of varying severity in 6 study volunteers. Previous studies using monkeys did not show any adverse effects; in humans, however, a cytokine storm and systemic inflammatory response syndrome were observed.

This overwhelming response of the immune system demonstrates its fragility but can also provide ideas for potential weapons. New immunological findings and studies with new drugs are providing a wealth of information about how to treat illnesses and various diseases, but in the future, the same information could be used to develop weapons. Using published data from new discoveries may enable the attachment of proteins to nanoparticles to achieve the overstimulation or suppression of the immune system. The same methodologies described in *Novel Nanotechnology-Enabled Biochemical Weapons* section would be utilized to defeat countermeasures. The difference would be in the choice of the specific protein, DNA, or RNA. Such an agent would be devastating, given the speed with which it could act and the intensive medical support required to treat it. Because the effects of inhaling or ingesting any amounts of these types of agents are not known, this weapon may most likely be used for targeting specific individuals unless operationalized for wider dissemination.

In response to nanoenabled threats that interfere with therapeutics, a potential countermeasure may be to develop nanomaterials that can be made to hold different targeting ligands or drugs in multifunctional ways or to develop a cocktail of nanomaterials that target various organs or deliver different drugs. Counter agents may be needed to block the cell receptor sites that are targeted by the threat agent. A nanomaterial and ligand may be designed to be delivered sublingually, by inhalation, or by gut. Rapid identification of the nanoparticle, however, would be critical – as well as its target and the drug payload – before administering the nanoscale counter agent or counter agent cocktail. Just as orthogonal detection schemes are needed, orthogonal treatment modalities will likely also be needed to deal with nanoenabled threats.

Self-Assembled Materials and Devices and Potential Molecular Assemblers

Molecular self-assemblers, or nanomachines, capable of assembling themselves, whether spontaneously or via some designated external signal, have sparked speculation, curiosity,⁴⁰ and occasionally dismissive amusement in the scientific community⁴¹

and controversy as well as fearful speculation in some parts of the nonscientific community. Conceptually mimicking the synthesis of enzymes, DNA, and other biochemical moieties, these self-replicating nanomachines were hypothesized in 1981,⁴² and remain unrealized today. The debate on the feasibility of molecular-scale mechanical creatures (“molecular assemblers”) continues to be unresolved,⁴³ while Drexler has professionally reemphasized the fundamental limits of physics relating to nanoengineered devices, he is now emphatically distancing himself from the self-replicating “nano-bots” notion while still advocating for consideration of safety in generation of nanoassembled material,⁴⁴ and he acknowledges the unexpected and unintended hyperbole that arose with the “grey goo” concept.⁴⁵ Nongovernmental groups have become the main proponents (and sometimes critics) of the notional concept of molecular nanotechnology.⁴⁶ Nonetheless, molecular self-assembly remains a topic of policy discussion,⁴⁷ and it is critical to delineate the science and technological applications from the hyperbole.

Biologists and chemists have long recognized the potential utility of self-assembly and self-organization. A substantial body of literature on chemical and biological self-assembly or self-organization has been amassed over the last 30 and more years.⁴⁸ Self-assembly can be described by imagining a box containing pieces of a jigsaw puzzle. The box is shaken, and when it is opened, the puzzle is complete and functional.⁴⁹ Self-organization of DNA and RNA through base-pairs interactions – hydrogen bonding, π - π electron overlap, multiple weak van der Waals interactions, and coordination bonding – is a fundamental part of all life on Earth. Molecular recognition, the basis for many diagnostic sensors, in many cases derives specificity from the analytes’ preferential interaction with the substrate, which is akin to the thermodynamic and kinetic driving forces for self-assembly in larger systems. The overwhelming majority of synthetic self-assembled systems and materials known today have been produced in aqueous or other solutions. In addition, current fabrication methods are largely limited to single batch processing, which is sensitive to initial and final conditions.

Biological self-assembly in conjunction with nanotechnology is an emerging active area of research in the fields of nanoelectronics, magnetic materials, and plasmonics, where the capability exists to create complex abiotic systems with molecular-level spatial precision and structural tunability.^{50–52} Nanoarchitectures composed of biological entities with one-dimensional CNTs, both single and multiwalled, inorganic nanotubes, and other nanostructures are being explored for nanoelectronics applications.⁵³ Biological linkers, such as DNA, RNA, and proteins (e.g., streptavidin), offer specificity for the unique labeling of carbon on inorganic nanotubes that are assembled on conventional substrates. Biological entities may also serve as insulators for engineering purposes. Current limitations include slow throughput, high costs, lack of selectivity, the lack of precise error correction, and the overall need for integration. Advances in these are likely, as well as biologically inspired cellular arrays are expected to be developed in the next 10 years.

There is no evidence that abiotic or mechanical self-replicating synthetic self-assembly will exist by 2030, and it may not exist in 2050. Self-replicating

biological systems exist today, and it is likely that more control and understanding of these mechanisms will be developed by 2030. Synthetic systems will exist with very limited functionality, and are expected to aid in assembling material using biochemical means. Artificial and modified biological systems will be commonplace in 2030.

Notes and References

1. Hammes TX (2007) Fourth Generation Warfare Evolves, Fifth Emerges, *Mil. Rev.* May-Jun.: 14–23. <http://usacac.army.mil/CAC/milreview/English/MayJun07/Hammes.pdf>
2. The White House (2006) Prevent Our Enemies from Threatening Us, Our Allies, and Our Friends with Weapons of Mass Destruction, <http://www.whitehouse.gov/nsc/nss5.html>
3. National Research Council (2006) A Matter of Size: Triennial Review of the National Nanotechnology Initiative. National Academy Press, Washington DC.
4. Ding SY et al. (2003) Quantum dot molecules assembled with genetically engineered proteins. *Nano. Lett.* 3:1581–1585.
5. Williams E, Abarbanel H, Alivisatos P, Block S, Brenner M et al. (2002) Opportunities at the Intersection of NanoSci., Biology and Computation, The MITRE Corporation; McLean, VA, JSR-02–300, Nov. <http://www.fas.org/irp/agency/dod/jason/nanoint.pdf>
6. Medina C et al. (2007) Nanoparticles: Pharmacological and toxicological significance. *Br. J. Pharm.* 150:552–558.
7. Tan BH, Tam KC (2007) Review on the dynamics and micro-structure of pH-responsive nano-colloidal systems. *Adv. Colloid Interface Sci.*
8. Pantarotto DR, Singh D, McCarthy M, Erhardt JP, Briand M, Prato KK, Bianco A et al. (2004) Functionalized carbon nanotubes for plasmid DNA gene delivery. *Angew. Chem.* 43:5242–5246.
9. Kam, NWS and Dai HJ (2005) Carbon nanotubes as intracellular protein transporters: Generality and biological functionality. *J. Am. Chem. Soc.* 127(16):6021–6026.
10. Fong CL and Hui KM (2002) Generation of potent and specific cellular immune responses via in vivo stimulation of dendritic cells by pNGVL-3-hFlex plasmid DNA and immunogenic peptides. *Gene. Ther.* 9:1127–1138.
11. Kam NWS and Dai HJ (2005) Carbon nanotubes as intracellular protein transporters: Generality and biofunctionality. *J. Am. Chem. Soc.* 127:6021–6026.
12. Tiwari SB and Amiji MM (2006) Improved oral delivery of paclitaxel following administration in nanoemulsion formulations. *J. Nanosci. Nanotech.* 6:3215–3221.
13. Oberdorster G, Sharp Z, Atudorei V, Elder A, Gelein R, Kreyling W, Cox C et al. (2004) Translocation of inhaled ultrafine particles to the brain. *Inhal. Toxicol.* 16:437–445.
14. Dan Luo W, Saltzman M et al. (2000) Enhancement of transfection by physical concentration of DNA at the cell surface. *Nat. Biotech.* 18:893–895.
15. Niidome T and Huang L (2002) Gene therapy progress and prospects: Nonviral vectors. *Gene. Ther.* 9:1647–1652.
16. Vijayanathan V, Thomas T, Thomas TJ et al. (2002) DNA nanoparticles and development of DNA delivery vehicles for gene therapy. *Biochem.* 48:14085–14094.
17. Marwick C (2003) *Br. Med. J.* 326:181; Dobson J (2006) Gene therapy progress and prospects: Magnetic nanoparticle-based gene delivery. *Gene. Ther.* 13(4):283–287.
18. Durcan N, Murphy C, Cryan SA (2008) Inhalable siRNA: Potential as a therapeutic agent in the lungs. *Mol. Pharmaceutics ASAP Article*, available at <http://pubs.acs.org/cgi-bin/sample.cgi/mpohbp/asap/html/mp070048k.html> Accessed June 30, 2008.
19. Doyle JM (2006) What race and ethnicity measure in pharmacologic research. *J Clin Pharmacol* 46:401.

20. For some examples, see: Vijayanathan V, Thomas T, Thomas TJ et al. (2002) DNA nanoparticles and development of DNA delivery vehicles for gene therapy. *Biochem.* 48:14085–14094; Dobson J (2006) Gene therapy progress and prospects: magnetic nanoparticle-based gene delivery. *Gene. Ther.* 13:283–287; Nel A, Xia T, Madler L, Li N et al. (2006) Toxic potential of materials at the nanolevel. *Science.* 5761:622–627; MIT Environmental Programs (2006) Potential risks of nanomaterials and how to safely handle materials of uncertain toxicity. http://web.mit.edu/environment/pdf/Nanomaterial_Toxicity_EHS.pdf; Lam CW, James JT, McCluskey R, Arepalli S, Hunter RL et al. (2006) A review of carbon nanotube toxicity and assessment of potential occupational and environmental health risks. *Crit. Rev. Toxicol.* 36:189–217; Maynard AD, Aitken RJ, Butz T, Colvin V, Donaldson K et al. (2006) Safe handling of nanotechnology. *Nat.* 444:267–269; Holsapple MP, Farland WH, Landry TD, Monteiro-Riviere NA, Carter JM, Walker NJ, Thomas KV et al (2005) Research strategies for safety evaluation of nanomaterials, part II: Toxicological and safety evaluation of nanomaterials. Current challenges and data needs. *Toxicolo. Sci.* 88:12–17; Service RF (2003) Nanomaterials show signs of toxicity. *Science* 300:243.
21. National Nanotechnology Initiative (2006). Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials. http://nano.gov/NNI_EHS_research_needs.pdf
22. Oberdorster G, Oberdorster E, Oberdorster J (2007) Concepts of nanoparticle dose metric and response metric. *Environ. Health Perspect.* 115:A290.
23. Poland CA et al. (2008) Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. *Nat. Nanotech.* doi:10.1038/nnano.2008.111.
24. Maynard A (2006) Nanotechnology: A research strategy for assessing risk, woodrow wilson center project on emerging nanotechnologies. http://www.nanotechproject.org/file_download/77
25. Medina C et al. (2007) Nanoparticles: Pharmacological and toxicological significance. *Br. J. Pharm.* 150:552–558.
26. Oberdorster G, Oberdorster E, Oberdorster J (2007) Concepts of nanoparticle dose metric and response metric. *Environ. Health Perspect.* 115:A290.
27. Bermudez E, Mangum JB, Wong BA, Asgharian B, Hext PM, Warheit DB, Everitt JI et al. (2004) Pulmonary responses of mice, rats, and hamsters to subchronic inhalation of ultrafine titanium dioxide particles. *Toxicol. Sci.* 77:347–357.
28. Ramires PA, Romito A, Cosentino F, Milella E et al. (2001) The influence of titania/hydroxyapatite composite coatings on in vitro osteoblasts behaviour. *Biomater.* 22:1467–1474.
29. Renwick LC, Donaldson K, Clouter A et al. (2001) Impairment of alveolar macrophage phagocytosis by ultrafine particles. *Toxicol. Appl. Pharm.* 172:119–127.
30. Nel A, Xia T, Madler L, and Li N (2006). Toxic potential of materials at the nanolevel. *Science.* 5761:622–627. <http://www.sciencemag.org/cgi/reprint/311/5761/622.pdf>
31. Long TC et al. (2006) Titanium dioxide (P25) produces reactive oxygen species in immortalized brain microglia (BV2): Implications for nanoparticle neurotoxicity. *Environ. Sci. Technol.* 40:4346–4352.
32. Long TC et al. (2006) Titanium dioxide (P25) produces reactive oxygen species in immortalized brain microglia (BV2): Implications for nanoparticle neurotoxicity. *Environ. Sci. Technol.* 40:4346–4352.
33. US Air Force Doctrine Document 2-1.8 (2004) Counter-Chemical, Biological, Radiological, and Nuclear Operations. <http://www.fas.org/irp/doddir/usaf/afdd2-1-8.pdf>.
34. Pister KSJ, Kahn JM, Boser BE et al. (1999) Smart dust: Wireless networks of millimeter-scale sensor nodes. *Electro. Res. Lab. Res. Sum.*
35. Mourez M et al. (2001) *Nat. Biotech.* 19:958–962.
36. Pannifer AD et al. (2001) *Nature* 411:229–233.
37. Abrami L, Fivaz M, Glauser PE, Sugimoto N, Zurzolo C, van der Goot FG et al. (2003) Sensitivity of polarized epithelial cells to the pore-forming toxin aerolysin. *Infect. Immun.* 71:739–746.
38. Abrami L, Liu S, Cosson P, Leppla SH, van der Goot FG et al. (2003) Anthrax toxin triggers endocytosis of its receptor via a lipid raft-mediated clathrin-dependent process. *J. Cell. Biol.* 160:321–328.

39. Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner MD, Panoskaltsis N et al. (2006) Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. *N. Engl. J. Med.* 355:1018–1028.
40. Freitas RA Jr. and Merkle RC (2004) Kinematic self-replicating machines, *Landes BioSci.*, Georgetown, TX <http://www.MolecularAssembler.com/KSRM.htm>
41. Moskovits M (2006) Nanoassemblers: A likely threat? *Nanotech. Law Bus.* 4:189–197.
42. Drexler KE (1981) Molecular engineering: An approach to time development of general capabilities for molecular manipulation. *Proc. Natl. Acad. Sci.* 78:5275–5278.
43. Baum R (2003) Nanotechnology: Drexler and Smalley make the case for and against “molecular assemblers.” *Chem. Eng. News* 81:37–42. <http://pubs.acs.org/cen/coverstory/8148/8148counterpoint.html>
44. Phoenix C and Drexler KE (2004) Safe exponential manufacturing. *Nanotech.* 15:869–872, http://www.iop.org/EJ/article/0957-4484/15/8/001/nano4_8_001.pdf
45. Drexler KE (2007) The Road to Advanced Nanotechnologies, Presentation at the National Academy of Science Sackler Colloquia on Nanomaterials in Biology and Medicine: Promises and Perils, Washington, DC. 10–11 April 2007, http://www.nasonline.org/site/PageNavigator/SACKLER_nanoprobes_program
46. These include the Foresight Institute, the Institute for Molecular Manufacturing, the Center for Responsible Nanotechnology, and The Lifeboat Foundation.
47. National Research Council (2006) Molecular Self-Assembly in a Matter of Size: Triennial Review of the National Nanotechnology Initiative. National Research Council, Washington, DC, pp. 99–109.
48. For some examples, see: Lehn J-M (2002) Toward complex matter: Supramolecular chemistry and self-organization. *PNAS.* 99:4763–4768; Whitesides GM and Boncheva M (2002) Beyond molecules: Self-assembly of mesoscopic and macroscopic components, *PNAS.* 99:4769–4774; Lehn, J-M (1995) *Supramolecular Chemistry: Concepts and Perspectives* (VCH, New York); Atwood JL, Davies JED, MacNicol DD, Vögtle F, Lehn J-M et al. (eds.) (1996) *Comprehensive Supramolecular Chemistry* (Pergamon, Oxford); Hof F and Rebek J Jr. (2002) Molecules within molecules: Recognition through self-assembly. *PNAS.* 99:4775–4777; Diederich F and Felber B (2002) Supramolecular chemistry of dendrimers with functional cores. *PNAS.* 99:4778–4781; Fréchet JMJ (2002) Dendrimers and supramolecular chemistry. *PNAS.* 99:4782–4787; Davis AV, Yeh RM, Raymond KN et al. Supramolecular assembly dynamics. *PNAS.* 99:4793–4796; Balzani V, Credi A, Venturi M et al. Controlled disassembling of self-assembling systems: Toward artificial molecular-level devices and machines. *PNAS.* 99:4814–4817; Cotton FA, Lin C, Murillo CA et al. The use of dimetal building blocks in convergent syntheses of large arrays, *PNAS.* 99:4810–4813; Roco MC (2003) Nanotechnology: Convergence with modern biology and medicine. *Curr. Opin. Biotech.* 14:337–346.
49. Professor Cengiz Oskan (30 January 2007) UC-Riverside at Nanotechnology for Chemical and Biological Defense 2030 Workshop, Santa Fe, NM.
50. Braun E and Keren K (2004) From DNA to transistors. *Adv. Phys.* 53:441–496.
51. Lee J, Hernandez P, Lee J, Govorov AO, Kotov NA et al. (2007) *Nat. Mater.* 6:291–295.
52. Maye MM et al. (2007) DNA-regulated micro- and nanoparticle assembly. *Small* 3:1678–1682.
53. Wang X, Liu F, Andavan GTS, Jing X, Singh K, Yazdanpanah VR et al. (2006) Carbon nanotube–DNA nanoarchitectures and electronic functionality. *Small* 11:1356–1365.

Chapter 5

Strategic Research Priorities and Directions

Formidable technical challenges exist in achieving the countermeasures envisioned for chemical and biological (CB) defense by 2030 projected in Chap. 3 and to enable countermeasures against the type of threats described in Chap. 4. Real scientific breakthroughs will be needed at a fundamental level in order to realize these revolutionary countermeasures in physical protection, detection and diagnostics, decontamination, and medical applications. Much of the research required for this broad strategy must be aimed at new scientific discovery versus research aimed at development of a specific application.

The nature of research is sometimes complicated by traditional disciplinary labels. As such, not all of the research directions described here will be labeled “nanotechnology” or CB defense. A primary example of this is transformative research aimed at understanding biological complexity. Success in this area will allow devices to mimic biological processes at the nanoscale, an extreme challenge requiring long-term commitment to high-risk and focused interdisciplinary research that will have profound impact on many aspects of CB defense. This type of challenge exemplifies the importance of setting flexible, science-based objectives rather than being driven by engineering deliverables (specific products or discrete capabilities) in the first 10 years of such an ambitious effort. Flexibility and proactive science-based program management is crucial. Forcing the science to conform to traditional or fit into a mold developed for engineering program management practices will be counterproductive to the goal of realizing revolutionary capabilities. To this end, active science-based program management in fostering scientific breakthroughs is central to the strategic research directions.

The eight overarching and cross-cutting strategic research priorities discussed here must each be addressed to achieve effective CB countermeasures by 2030. To make this happen, collaborative groups of scientists, researchers, and application experts in each area must translate each strategic direction into a detailed tactical roadmap. An important aspect of the 2030 goals for each research area is that they are not straight-forward “low hanging fruit” and the pathways to achieve them are not currently clear. Therefore, as discoveries are realized, each roadmap will change and grow.

Hurdles and bottlenecks are to be expected in any area of discovery-based research. To achieve this level of progress, researchers cannot rely on mock “sys-

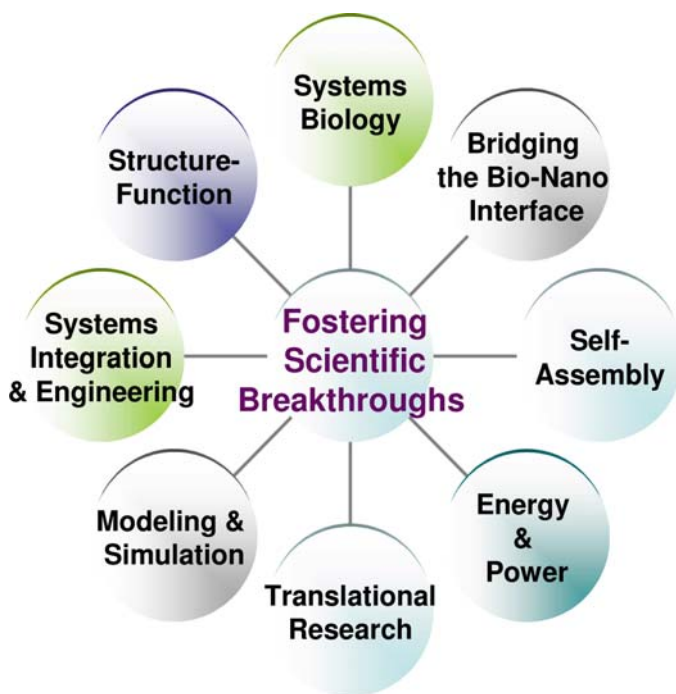


Fig. 5.1 Eight strategic research goals needed to realize revolutionary chemical and biological countermeasures for 2030. Intentional effort to foster scientific breakthroughs is crucial in order for each strategic research to be successful and for the overall development of revolutionary defense capabilities

tems engineering” that merely combines existing commercial off-the-shelf technologies or cobbles together technologies at disparate stages of development. Instead, each of the eight major priorities must be both interdisciplinary— individual projects are likely to be disciplinary at the onset - and driven, as shown in Fig. 5.1, by methods and intentional program management designed to foster scientific breakthroughs. Such aggressive targets will require both revolutionary ideas and interconnected efforts to achieve them.

This approach to interdisciplinary research must be increased for basic research through advanced technology development.¹ If set in motion today, such strategic research programs would enable the capabilities envisioned for 2010, 2020, and 2030 and would be able to protect against the type of threats imagined in 2030. Toward achievement of those revolutionary countermeasure capabilities, the eight strategic research directions discussed are crucial. While some research directions may superficially seem to be oriented to one capability or another, they are truly intended to be overarching research directions and are integral in some large or small manner to the realization of each and all of the desired revolutionary capabilities. The order presented is intentional and reflects the prioritized rankings by study and workshop participants for realization of 2030 revolutionary countermeasures

(as described in Chapter 3) and ability to enable countermeasures against the type of nanotechnology-enabled threats (as highlighted in Chapter 4). The strategic research directions were based on both consideration of desired countermeasure capabilities described in Chapter 3 and capabilities that would be needed to defend against the type of threats described in Chapter 4. The strategic research directions reflect scientific importance and technical challenge as well as importance in enabling national security in the future.

Structure and Function of Nanomaterials

A number of basic research directions are needed to successfully design nanomaterials with structures and functions that both enable revolutionary CB countermeasures and that are appropriate for use in these applications.

Understanding and Controlling Nanoscale Properties and Reactivity

The ability to understand the relationship between the structure and the function of nanomaterials – whether bionanomaterials, inorganic nanomaterials, or hybrids – is a cornerstone for all of the 2030 countermeasures. Nanomaterials have shown a number of novel physical and chemical properties and functions that are different from those of bulk substances. Significantly more fundamental knowledge, however, must be gained before rational, predictable synthetic protocols toward desirable properties will be possible. Desired research efforts to understand and control the chemical and physical properties of nanomaterials – effects, phenomena, properties, and performance – include the following. Note that a near-term need is for computational modeling and methodology that can aid in predicting properties of certain nanostructures.

- *Mechanical properties.* Many of the mechanical properties of nanoscale materials are changed from the bulk, including elastic modulus, fracture toughness, wear resistance, fatigue resistance, and hardness. As a result of altering a material's structure or composition at the nanoscale, properties such as energy dissipation and linearity of properties can be designed. Research in this area begins with measuring and modeling the size and shape of nanoscale particles, and also includes the size and shape of nanoscale pores. These properties may directly affect all other functional properties.
- *Electrical properties.* The large surface-to-volume ratio in nanomaterials means they can hold considerably more energy than bulk crystals. This can lead to new dielectric or electronic properties linked to their large surface or grain boundary area.

- *Optical and photonic properties.* The efficiency of charge transfer over nanoscale distances and the quantum confinement of electrical carriers within nanoparticles are two factors that make nanomaterials optically different from bulk crystals. Nanophotonic properties can be linear and nonlinear, and can be finely tailored by controlling material dimensions and surface chemistry. Distinct color indicators may be based on surface plasmons; the light output is dictated by the dielectric function of a nanomaterial and the shape of a nanoparticle. Specific needs include reactivity of nanoscale materials to electromagnetic radiation, including photoreactivity.
- *Magnetic Properties.* The coercivity and saturation magnetization values that describe the strength of a magnet may increase with a decrease in the grain size and an increase in the specific surface area of grain boundaries. The scale of magnetic domains may also adversely affect magnetism at the nanoscale. Research is needed in reactivity of nanoscale materials to magnetic fields.
- *Chemical properties.* Increased surface area increases the chemical activity of a material. For example, a metal in bulk form may not be a catalyst; the same metal in nanoscale particles may be an excellent catalyst. Important research measures pH, oxidation and reduction characteristics, and surface properties. An important concern is how nanostructures can change the chemical mechanisms of such key processes as hydrolysis and catalytic responses as well as differing hydrophobic, hydrophilic, or amphipathic surface properties. The atomic structures of high-energy surface sites and various types of defect sites on nanocrystals are needed, as well as their effect on reactivity. An initial priority is to gain exploitable knowledge of the physical chemistry of various nanoparticle surfaces.
- *Thermodynamic parameters.* This includes precise measures for enthalpies and free energies of formation of nanoscale materials where they differ from large crystals.

Two overarching needs are the ability to synthesize of all types nanomaterials and the fundamental understanding of the dynamics, kinetics, and mechanisms of their formation, along with understanding of how to maintain and optimize a variety of structural and functional properties during synthesis. This may range from simply designing desired porosity to manufacturing very large quantities of nanomaterials efficiently for use in wide-area outdoor decontamination and demilitarization.

Fabrication needs also include the ability to combine organic and inorganic nanoparticles into hybrid materials. For example, organic clathrates, binders, and basket-shaped molecules – such as block copolymers and triblock polymers – may be combined with inorganic oxides, polyoxometallates, and chemically aggressive porous materials to form useful hybrids. This is important in the development of countermeasures that can select, detect, and decontaminate a wide range of toxic materials.

Ultimately, nanomaterials are expected to be integrated into the design of a variety of precoats, protective suits, multifunctional materials, and medical devices. They may employ interactive nanotechnology systems that communicate by electronic, optical, or magnetic signaling. Systems may also, for example, utilize smart inorganic and organic synthetic membranes with gated porosity and

semipermeable technology. With tailorable properties, functional and structured nanomaterials can form the basis for a revolutionary shift in CB defense.

Ready examples for exploitation include nanoscale materials with desired particle size and dispersion properties that may be delivered as aerosols or powders will be needed for indoor decontamination. Nanoscale materials with designed structural reaction kinetics may be used for passivation of biohazards, and nanoscale catalysts may be used for gelation or for polymerization of chemical agents. Nanoscale materials with designed surface adhesion may be used to defeat encapsulated toxins or novel agents, either by coating of the protective capsule to disable it (“trap and coat”) or by removal of the capsule and deactivation of the exposed toxin (“trap, strip, and kill”). Such materials would need adhesive properties appropriate to interact with a variety of encapsulating agents – sugars, polymers, lipids, liposomes, hydrocarbons, and silica. Nanomaterials may be designed to decontaminate highly toxic chemical or biological agents, prions, and toxic nanoparticles.

Understanding Properties and Reactivity Related to Physiology

Along with research on the physical and chemical properties of nanomaterials, simultaneous and coordinated research is needed on their physiological properties, and any associated environmental, health, and safety risks. At the nanoscale, research must address the correlation between factors such as particle size, shape, surface charge, area, and reactivity and potential toxicological risks.

The toxicological response of most nanomaterials for humans and animals is currently unknown. Fundamental research to identify indicators of more general negative consequences of types of nanoscale structure is important. Concerns include possible allergenic and neurological effects, blood–brain barrier transport issues, and the persistence and ultimate fate of nanomaterials in organisms and the environment. This research area is a priority to enable the design and use of countermeasures to make them both more difficult to misuse or disable and to mitigate any potential health risks or unintended environmental consequences. For example, the selection of or the means of targeting one node of interaction versus another may make a countermeasure more robust or may reduce side effects. An important point of reference is to learn from how industry has learned how to handle known toxic materials safely.

Different methods of delivery of nanotechnology-enabled CB weapons will likely require different countermeasures. Delivery via aerosol, food, water, or skin will potentially elicit different physiological and biological reactions and will require different treatments. For example, prions and other proteins may be able to attach to nanoenabled aerosol particles that have the capability to cross the blood–brain barrier. Research to understand delivery mechanisms for prions, levels of infectious doses, and overall time dependence is needed.

Selective bioaccumulation, or an accumulation process in which biological sequestering results in a higher concentration of a substance in one location, is

another essential focus area for Environmental Health and Safety study. The pattern of bioaccumulation of a nanomaterial may depend on the delivery methods, such as respiration, ingestion, epidermal contact, or other methods.

A number of existing federal research programs may be leveraged to jump start understanding needed for CB defense research programs. These include the National Toxicology Program (NTP),² the Nanotechnology Characterization Laboratory (NCL),³ the National Institute for Occupational Safety and Health (NIOSH),⁴ and the research needs as identified through the National Nanotechnology Initiative (NNI).⁵ Industry and NGO consortia such as for nanomanufacturing⁶ and the International Council on Nanotechnology (ICON)⁷ are also useful starting points. The Office of the Secretary of Defense's Emerging Contaminant's Nanomaterials Working Group serves as the DoD's coordinating body for engineered nanomaterials-related environmental, safety, and occupational health technical, policy, and legal information.⁸ These efforts may uncover possible indicators of unexpected toxicological effects and other health and environmental consequences attributed to nanostructures. A DoD laboratory with the explicit mission to monitor other federal, industrial, and global programs could effectively leverage these efforts.

Systems Biology

Systems biology is the integrated discovery, characterization, and understanding of the interactions between components of a biological system. The study of systems biology has experimental, computational, and theoretical components, involving measurement, data mining, modeling, and manipulation.⁹ It involves an integration of molecular biology (information transfer), physiology (adaptive states), developmental biology (physiological growth), and evolutionary biology (natural selection). The study of systems attempts to address all these through quantitative measurement, modeling, reconstruction, and theory.¹⁰

The multivariate nature of systems biology requires an interdisciplinary approach to discovery, incorporating chemistry, physics, engineering, computer science, informatics, statistics, computational modeling, and biological sciences in pursuing integration of “-omics”-related technologies. For nanosystems, systems biology is a method to gain understanding of the translation from biological systems to multifunctional nanomaterials resulting in the mimicking of chemical or biochemical interactions through design and engineering of biotic or abiotic materials and systems. It is important to understand the connectivity between biological pathways in order to effectively counterthreats from the malicious use of biotechnology. Using a systems biology approach, it may be possible to find the nodes of interaction among various pathways and CB agents. Classic indicators include up- or downregulation of transcription or translation of different genes within a given cell type and cell surface markers for determining interactions between different cell types *in vivo*. Nanoenabled countermeasures may then be targeted to these nodes of interaction (e.g., a binding pocket of a critical protein) for diagnostic, preventative, or therapeutic purposes.

Systems biology threads through many of the revolutionary countermeasures envisioned for 2030, most prominently detection, diagnostics, and medical countermeasures. For example, sentinel programs aimed at molecular surveillance of animal or plant populations requires an understanding of molecular processes at the systems level. Once an array of signatures is discovered and validated, molecular recognition or sensing elements can be developed for diagnostic assays. Presymptomatic disease detection and design of an artificial immune system require an in-depth knowledge of a host's molecular processes in response to various threats or external stimuli. An understanding of these processes will then allow insight into the requirements of engineered materials for mimicking the immune system.

Although the recent developments of advanced techniques in high-throughput measurements of proteins, RNA, and DNA have provided many opportunities in systems biology, it is still in its infancy in terms of concept and in enabling “-omics” molecular profiling technologies. In the very near term, 2010, an integrated, interdisciplinary, colocated research effort needs to be erected for the singular purpose of developing 2030 threat agent countermeasures. Development of these countermeasures via systems biology will include major research thrust areas in computational science and modeling, hardware and platform development, and biological model development.

It will be important to establish and devise computational approaches in conjunction with experimental approaches – eventually, a hybrid approach will be necessary to explain and predict the behavior of complex biological organization and processes in terms of the molecular constituents. Computational modeling of nanoenabled biological systems will require a different approach, as biological systems are dynamic, constantly changing between different states. Therefore, innovative software and other computational tools must be developed that appropriately simulate such systems. Experiments will need to be devised that will refine these computational models and approaches.

There are many technical hurdles to overcome in systems biology applications, including the enhancement and development of appropriate animal models and animal studies; data mining and data analysis of massive data sets from proteomics, genomics, and metabolomics studies; data synthesis from different studies and different experimental technologies; statistically relevant molecular signature validation; and translation of molecular signatures to sensor platforms. The research needed to overcome these hurdles will need to focus on the understanding of the mechanisms of pathogenicity and triggering host responses; sample preparation, stabilization, and concentration; signal recognition; hardware integration; bioelectronic interface; integrated hardware platforms for support; identification and tracking mechanisms and devices that can self report; robust ligand manufacturing; multimode integration; and biologic compatibility.

In addition, intra- and intercellular communication and social behavior of infection and transfection processes will need to be studied, as well as building platforms for measurement of mechanical and surface shape, time-resolved protein and gene expression and signaling, and multiple communication mechanisms observed in individual cells and in colonies (e.g., optical, chemical, mechanical, electrical, signal transduction, characterization, cytokine, toll receptors, and other

regulators). By understanding these communication processes and mechanisms, as well as cellular interactions with specific agents, information and network operations modeling systems can be developed, as well as synthetic system modeling, biomimetics, and experiments for early response triggers. Cellular sensors can be designed through *in vitro* stabilization of cellular and intracellular material and matrix and interfacing this cellular material (organic and inorganic materials) to platforms. Once prototypical model systems are developed and tested, then prototype sensors can be built.

A common bottleneck in similar large-scale efforts is the ability to get quantitative data from many different experiments, models, and conditions. Nanoscale technologies may aid in this cause, for example, the development of integrated nanoelectronics-based microfluidic devices would allow for automated testing and collection of voluminous combinatorial data sets. Such technology developments would lead to a library array of known characteristics and signatures, for example, a library of host responses to pathogens and a library of pathogen responses (metabolic pathways). These libraries would then help provide a baseline for anomaly detection to minimize effects and early response. Furthermore, the application of systems biology to identify cellular responses to be used as fast, multidimensional detectors would provide many targets and sensors for anomaly detection.

Systems biology will have to integrate both a top-down approach utilizing high level -omics and a bottom-up approach utilizing advances in reconstruction and design of new biological parts, devices, and systems. Biomimetic materials will need to be synthesized and designed, which will require an understanding at the molecular level; regenerative materials and multifunctional materials will have to be biocompatible. Finally, computational modeling will need to be integrated for structure design.

Many research programs driven by systems biology face common problems. Complex systems with many variables lead to a noisy environment, making it difficult to achieve accuracy and sensitivity of measurements. The large number of measurements required makes it imperative to keep the cost per measurement as low as possible. Also, as information becomes increasingly viewed as a commodity of value, rights and restrictions to data access come with associated costs and complications.

Knowledge of biological pathways in normal and disease states is ripe for clinical application. Obtaining and applying this knowledge, however, is difficult due to interrelated pathways and the sheer number of variables (genes, gene products, time progression, physiological, environmental factors, etc.) in a given system.

The Interface with Biological Systems: “Bridging the Bio- and Nano Worlds”

Biological systems are well-polished machines, providing effective, highly redundant, and error-correcting processes and mechanisms, so it only makes sense to leverage millions of years of Mother Nature’s work toward developing CB defense systems.

The development of biological threat recognition and identification capabilities will require using naturally created inorganic components to interface or influence biological systems or biological components to influence abiotic systems or to read and generate biological signals. Injecting signal information or energy into the cell as electrical potential, gradient transport, and ion exchange mechanisms or influence biological behavior by external signals or force is also possible. An additional application is probing cells with analytical tools and artificially created nanomaterials with minimal perturbation of cell function. Ultimately, researchers may seek to biomimetically simulating cell function by arraying cell motors, bioenergetics, or subcellular molecular assemblies on organic scaffolds.

A major challenge is probing cells with analytical tools and artificially created nanomaterials with minimal perturbation of cell function or impact on cell viability. The potential to impact biocompatibility and avoid biofouling highlights the importance of pattern recognition and signal processing, topics covered in details later in this chapter.

Biomimetic systems and devices as nonspecific indicators of threat and response might take the form of a "nanocanary," in which a few living cells are harnessed to monitor biological responses to a variety of biologically active test agents. Such biomarker systems would enable a wide spectrum of applications that are adaptable to a broad range of unknown threats, including implantable sensor devices with presymptomatic sensitivity to biomarkers. Therefore, one key to the development of biomimetic systems is to develop analytical tools that can probe *in vivo* and *in vitro* cellular processes at the molecular scale with minimal disruption of normal cell function.

Near-term milestones supporting the above long-term goals for bridging the bio-to-nano interface include, for example, attaching targeted molecules or functional groups to nanostructures; demonstrating autonomous motion in nanoparticles; or developing a sensor interface between blood and tissue. Accomplishing such near-term milestones could lead to scalable energy sources down to the nanoscale, a viable biotic-to-abiotic interface, analytical tools and techniques for applications at the nanoscale, and robust, controllable, and reproducible bio-based manufacturing techniques applicable to nanodevices.

The issue of biocompatibility must be addressed to ensure that nanoscale biotic constructs demonstrate viability, longevity, and shelf-life in the artificial environment of a deployable sensor. This is especially important for applications such as implantable sensor nanodevices, tissue engineering, and drug-delivery systems. Research to understand, predict, and enable to the ability to nanomaterials to interact without eliciting negative immune, systematic, or other cellular responses in performance as a substrate that will support the cellular activity and will facilitate molecular and mechanical signaling systems is needed.

For the revolutionary countermeasures to be realized, it will also be important to discover appropriate biomarkers that can transduce to abiotic signals. These could, for example, indicate the presence of biological or chemical agents. Research is also needed to integrate hybrid functions in bio-based nanoscale constructs for enhancing sensor specificity and signal transduction.

Although the benefits of such advances are clear for medicine and public health, it is important to consider that these same advances could also be designed to cause intentional harm. The same nanoenabled system that facilitates delivery of a vaccine, for example, can be used to deliver a biological agent. For this reason, researchers should consider the use of such technology in weapons and research countermeasures as necessary.

Self-Assembly, In Vivo and In Vitro

Self-assembly of complex materials and devices presents huge challenges in translating the principles and processes observed in biological systems to physical structures. Self-assembly is “the natural tendency of physical systems to exchange energy with their surroundings and assume patterns of structures of reduced free energy.”¹¹ Nontrivial differences exist between molecular self-assembly for the manufacture of simple materials and devices (i.e., “doorstops”) and the manufacture of complex materials and devices. Numerous examples exist for biological systems that employ molecular self-assembly in addition to a more integrated complex manufacturing process. It will be important to understand that these complicated processes to enable similar assembly of nanomaterials and nanodevices *in vivo*.

Many known self-assembly processes – quenching, solidification, crystallization, solution- and vapor-phase chemical reactions, and polymerization – occur in specific solution environments. For a self-assembly processes in an aqueous environment – as for most biological processes – a mix of appropriate conditions is required, for example, a narrow temperature range or reagent concentrations. It is therefore likely that environmental and experimental conditions will play an important role in synthesizing new nanomaterials and nanodevices with desired properties and functionalities.

A revolutionary research goal is a low-cost, high-volume self-driven production of a nanomaterial or nanodevice. An abiotic supramolecular self-replication process approach may be viable, but it is important to consider the complexity of such a system. For example, an increasing number of interoperable components implies a high error rate incurred during the self-assembly process. Biological systems have the ability to self-correct errors in molecular assembly, while abiotic systems do not. DNA repair mechanisms can recognize errors in base pairing, breaks, and altered bases, and then repair them. Such a self-recognition technique is a high priority to enable damage-tolerant nanomaterials and systems. This may also impact the ability for nanomaterials and nanodevices to self-repair.

Catalysts and enzymes present attractive applications for nanomaterials in the areas of decontamination and sensing due to their high reactivities. In addition, encapsulation for the purposes of stabilizing the function of catalysts could enable the extension of operation or duty cycle of catalysts. For these reasons, research in understanding how reactive sites on catalysts and enzymes function will greatly aid this goal.

Modeling and Simulation

In addition to the role of modeling and simulation complementary to the other strategic research directions, one intended goal by 2030 is to have an established technology base capable of producing nanomaterials that meet user design requirements. This will only be possible when the detailed science-based models and simulations are developed that will allow industry to design for capabilities and properties. Such models and simulations do not currently exist and represent a concerted challenge between now and 2030 to develop, test, verify, validate, and then accredit the use of such models for specific design functions.

Current atomic level modeling and simulation tools will have to undergo great enhancements and fundamental advancements in their functionalities to be able to provide the design capabilities to build the materials and sensors to defend against CB threats. The level of complexity, realism, and fidelity provided by the current physics and chemistry-based models and simulation must undergo a radical improvement to meet the future design requirements. Models must be developed for the more complicated biological and chemical entities that would be present as threats on the future battlefields. Models must also be created that will provide the basic design ability for the future nanoscale and hybrid materials that will be manufactured and provide the physical protection and detection from the threats. At the same time, models and simulations of the entire design process including the information exchange between models, materials, and sensors and of the behavior of materials must be developed at a scale that has never been implemented.

Interoperability and coupling of the various models and simulations across the different disciplines involved in the biological and nanoscale research initiatives must be assured in order to effectively benefit from advancements made in these fields. The problem facing the future integrators and architects is that many models and simulations cover too many entities, phases, scales, and processes. The need for a common framework that can provide a “backbone” for individual models is clear. Such a framework (or system of frameworks) could allow individual model development, and then facilitate coupling and interoperation to gain much deeper insight and understanding of a variety of processes modeled.

True interoperability will not be just a simple sharing of data and models. There must be a rigorous standardization to prevent misapplication of modeling results. Models and simulations at different scales must be correctly integrated. New scaling laws and rules will be required to translate model prediction at the nanoscale to the micro-, the meso- (or “middle” scale), and ultimately the macroscale. Numerical algorithms must be carefully documented to assure that issues of time steps, grids, and boundary conditions are appropriately applied for uses with other models and simulations experiments and projects.

Future advanced modeling and simulation initiatives to develop the code and tools required to design and manufacture materials and sensors that will have pre-determined properties will involve large teams of researchers, developers, systems engineers, program managers, and hardware and facilities. Development efforts of this magnitude will require massively parallel processing. The infrastructure

requirements will necessitate the expansion of the current supercomputing facilities to provide for more uses while being easier to use as well as faster code development and runtime. Perhaps most important, usable interfaces for all of these tools will result in more productive use of researchers' time.

Code team development and management practices that encompasses many different disciplines and subject matter will itself pose a serious management risk. Of growing importance are standard practices and processes for the care for and maintain model libraries, for porting codes across machines, and especially for methods to address code life cycle management issues.

Risks to the application and reliance on models must also be addressed. A rigorous verification, validation, and accreditation process will help to assure that the models and simulations are properly used for the intended applications. This process should be employed throughout the life cycle of the codes. For example, models that may be accredited for use at certain research level applications might not be approved for manufacturing scale applications.¹²

Ultimately, it will be the partnering between academia, industry, and the government that will establish the standards required for the development of high-reliability models and simulation for manufacturing. Standards-based models will be more willingly accepted by the broader development and manufacturing community allowing for faster advancements. It will be through these future models and simulations that are based on the emerging science of nanotechnology of today that we will be able to rapidly respond to future CB threats with the necessary materials and sensors that work together.

Power and Energy

Any autonomous nanoscale device or system will require a source of energy to sense, analyze, or communicate. Improved fundamental understanding of devices and components utilizing nanoscale technology for energy and power generation is needed to produce high-performance micro- and nanoscale devices and components. Advanced methods for design, modeling, and simulation of such devices and components are also desired to define new and improved capabilities and applications. Efficient and cost-effective experimental techniques for processing and fabrication are also needed. For purposes of persistent surveillance in CB defense, nanoscale self-sustaining, or renewable power sources would enable distributed networks, and could also significantly reduce the pack weight for mobile operators.

Continued advances in silicon nanoelectronics and beyond will enable developments in adaptive and reconfigurable devices. To enable energy-efficient operation, low-power and low-noise electronics are needed for novel network architectures and advanced systems that incorporate novel nanoelectromechanical systems (NEMS), nanosensors, and nanoactuators.

Several major areas for research were identified to help fulfill the power source needs for nanodevices and systems:

- *Energy scavenged from the environment.* This may include biological – flora and fauna – as well as nonbiological sources such as radiofrequency waves and the more traditional solar insolation.
- *Energy harvested from humans.* This may include energy derived from glucose or ATP, or mechanical energy from user motion – walking - and other processes.
- *Nanoenabled power generators* for field use, such as piezoelectric materials.
- *Miniature fuel cells.*

The potential for as-yet undiscovered energy storage technologies is high in this area owing to multiple commercial and government funding sources and multiple potential applications. Impacts of bio-powered MEMS and NEMS may include self-powering systems that use flexible “printable” electronics in sensors, functional devices that are transparent to visible light, generating electricity directly from biological systems, and implantation of flexible power sources in biological systems.

Systems Integration and Engineering

The CB defense infrastructure must be tightly integrated. Groups developing countermeasures and protection must work closely with those groups researching the potential CB weapons threats under development by other forces. Once the material properties, capabilities, and delivery options of potential threats are understood, they must be transitioned as input requirements to the groups developing the countermeasures, detection, and protection technologies. Likewise, the underlying technology developed for the detection and protection must be given to the groups who will identify potential countermeasures. The entire CB warfare effort must therefore be treated as an integrated system and initiate a systems integration early that shall be interactive and parallel with all research endeavors.

Systems integration and engineering must be applied early in the development life cycle for future defense technology from biological and chemical threats. Much of the functionality of an eventual defense system is a result of decisions made early in the procurement life cycle. It is critical to capture the design requirements early in order to direct the path of development to build the best overall system to meet the needs of the warfighter. Biological and chemical defense covers more specialized disciplines than any other defensive platform and therefore must be particularly vigilant to make sure that the multiple disciplines are integrated to assure that the separate components, sensors, and materials will work together and not add an additional logistics burden to the warfighter.

At a high level, three broad domains must be integrated during the development process of future defense technology from biological and chemical threat. There must be a process to integrate the development of the required materials to meet the

established requirements, the integration of the fundamental material properties used to design these desired future materials and sensors, and the information technology required throughout the life cycle of operation of the defensive system.

Materials integration must provide the capability to effectively work at multiple scales. Building new materials from the atomic level will require an integrated approach to designing at the nanoscale to meet requirements at the micro- and mesoscales. From the user's perspective, it is these larger scales that impact their decisions and needs. The big challenge then is to develop a process to capture these large-scale user's requirements and translate them into the science and engineering technical gaps that will be recognized by many different science and engineering disciplines.

In addition to integrating material interactions at different scales, biological systems that will be coupled to sensors pose additional challenges. There must be an integration of the material interactions between the soft, hard, and biological interfaces. This is an emerging field that will require additional research and development to optimize the coupling of such diverse materials and share information across the interfaces.

The development of the technologies related to biological and chemical defense will cross many scientific and engineering disciplines. While each group will not necessarily have direct interaction with one another, their material properties measurements will have to be exchanged among development groups. This will require integration across competencies conducting research and development that include basic scientists, engineers of nearly every discipline, and the industrial sector manufacturing the materials that either produce or use data across all fundamental material properties, including thermal, optical, electronic and electrical, surface science; chemical activity and reactivity; and biological properties.

This integration will require the development and implementation of "living" property databases. Entities are dynamically modified and more information become available and existing data are updated. Keepers of these databases must be concerned with an equally dynamic capability to provide timely verification, validation, and certification of these data. It is not just having access to the most recent data that is important, but rather to have access to the most recent certified data that will provide the greatest confidence among groups to share information.

The key enabling technology that will be the backbone to this dynamic exchange of data and systems engineering oversight of the different research and development efforts will depend on the sophistication of the information technology integration. Integration of information technology must provide guidance on database structure and development as well as interoperability. This functionality will be required throughout the life cycle of the systems starting with the early-stage "living" databases of material properties to the fielded information systems that are being utilized by the detection and physical protection systems. Key information integration efforts must include informatics, both internal and external networking and communication protocols, and data processing.

The integration of database development and integration of material properties discoveries must lead to a set of industrial standards and protocols that will provide

the standardization across the emerging nanomanufacturing industrial base. These industrial standards must apply to the different techniques capable of processing materials at different scales and applications, both fixed use and multiuse.

Translational Medicine

In addition to the discovery of fundamental medical science, additional research is needed to aid the transition of those discoveries toward the production of usable devices. As in any medical application, researchers must always consider the processes needed for clinical trials, whether the chosen vector is suitable for use in the body, and the potential for FDA approval and manufacturing scale-up.^{13,14}

This work, termed translational medicine, is needed to address new nanoenabled products, such as following:

- Convalescent sera (e.g., hyperimmunoglobulin) whose production can be rapidly scaled up to meet immediate threats,
- Nanoadjuvants that increase countermeasure efficacy, and
- Nanoparticles designed to adsorb CB moieties.

In parallel with developing convalescent sera or vaccines, it is important to develop advanced, rapid diagnostic devices that identify a specific threat agent. This basic information would be required for prevention, detection, diagnosis, and therapy. Near-term technologies should be aimed at providing partial information immediately followed by a thorough evaluation.

Basic research directions include the development of nanoparticles that encapsulate nucleic acids and cytokine genes, for example, to target antigen-presenting cells. In addition, nanoparticles that display multifunctionality could be designed for combination therapy with a universal drug-delivery system. To support these goals, basic research is needed to understand the pathophysiology of the nanoenabled agents and countermeasures and the clinical relevance of measured or analyzed markers. Research to address understanding of a pathogen's traditional, engineered, or nanoenabled effect on molecular pathophysiology is a key component of this effort.

Many organizations will be useful partners in this research area, including academia and small biotechnology firms for basic research, small biotechnology firms, pharmaceutical companies, and DoD service laboratories for applied research, and Good Manufacturing Practices facilities for advanced technology development. DoD service laboratories may be useful for animal studies. A non-technical aspect to the transition of revolutionary ideas is to introduce and foster working relationships among all of these entities.

Enabling infrastructure may also be leveraged as part of basic and translational research efforts for nanotechnology-enable medical countermeasures for CB defense. As an example, a family of animal models that support the evaluation of nanomaterials needs to be established and integrated into the approval process.

Appropriate animal models need to be verified for nanomaterial flows, toxicity, pharmacokinetics, and immune response.¹⁵

The recent addition of nanomedicine to the roadmapping process at the National Institutes of Health has stimulated a considerable investment into nanoenabled approaches to medicine and health.^{16,17} The NIH investment, and the physical infrastructure accompanying the research funding, provides a valuable asset for the CB defense community to leverage.¹⁸

Notes and References

1. This refers to DoD science and technology (S&T) program categories of basic research (6.1), applied research (6.2), and advanced technology development (6.3).
2. The National Toxicology Program (NTP) has initiated efforts to examine a select representation of nanostructures – carbon nanotubes, fullerenes, nanostructured titanium dioxide (TiO₂), and zinc oxide (ZnO) particles used in sunscreens and bactericides, and quantum dots.
3. The Nanotechnology Characterization Laboratory (NCL) was established with assistance from the National Institute of Standards and Technology (NIST) and the Food and Drug Administration (FDA). The NCL serves as a resource and knowledge base for all cancer researchers to facilitate the regulatory review of nanotechnologies intended for cancer therapies and diagnostics. By providing the critical infrastructure and characterization services to nanomaterial providers, the NCL can accelerate the transition of basic nanoscale particles and devices into clinical applications. The NCL has developed a set of assay cascade protocols that allows for the characterization of nanomaterials' physical attributes, their in vitro biological properties, and their in vivo compatibility using animal models. The time required to characterize nanomaterials from receipt through the in vivo phase is anticipated to be one year. A robust bibliography of pertinent studies can be found at http://nano.cancer.gov/resource_center/scientific_bibliography.asp
4. Progress Toward Safe Nanotechnology in the Workplace NIOSH 2007-123. <http://cdc.gov/niosh/docs/2007-123/pdfs/2007-123.pdf>
5. Prioritization of Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials. http://www.nano.gov/Prioritization_EHS_Research_Needs_Engineered_Nanoscale_Materials.pdf
6. Nano Risk Framework, <http://www.nanoriskframework.com/page.cfm?tagID=1095>
7. (2008) Towards Predicting Nano-Biointeractions: An InterNatl. Assessment of Nanotechnology Environment, Health and Safety Research Needs. InterNatl. Council on Nanotechnology, Rice University, Houston, Texas; http://cohesion.rice.edu/CentersAndInst/ICON/emplibrary/ICON_RNA_Report_Full2.pdf ICON is “an international, multistakeholder organization whose mission is to develop and communicate information regarding potential environmental and health risks of nanotechnology, thereby fostering risk reduction while maximizing societal benefit.” More information available at <http://icon.rice.edu/index.cfm>
8. The Nanomaterials Working Group is cochaired by the Deputy Under Secretary of Defense, Laboratories and Basic Science [DUSD(LABS)] and the Deputy Under Secretary of Defense (Installations & Environment). More information can be found at <https://www.denix.osd.mil>
9. Henry CM (2003) Systems biology. *Chem. Eng. News* 81:45–55.
10. Kirschner MW (2005) The meaning of systems biology. *Cell* 121:503–504.
11. (2006) National Research Council. *A Matter of Size: Triennial Review of the National Nanotechnology Initiative*. National Academy Press: Washington, DC. p. 100.
12. Significant progress has been made to date in the practices applied to large-scale parallel processing to address national technological issues. An excellent example upon which to

expand for the future needs is that of the National Nuclear Security Agency (NNSA). The code development practices and testing procedures that have evolved over time for their nuclear mission provides a sound foundation for future expansion in developing the required biological and chemical defense related models and simulations. Their practices for lifecycle management of codes demonstrate the potential reliability resulting from rigorous uncertain qualification methodology development for high consequence national security decision making.

13. Schloss JA and Sieving PA (2006) Nanomedicine Roadmap Initiative, RFA Public Forum January 27, 2006.
14. US Department of Health and Human Services (July 2004) Cancer Nanotechnology Plan: A Strategic Initiative to Transform Clinical Oncology and Basic Research Through The Directed Application Of Nanotechnology, National Institutes of Health, National Cancer Institute.
15. The National Cancer Institute's National Characterization Laboratory could serve as a working example of a protocol that characterizes nanomaterials' physical attributes, their in vitro biological properties, and their in vivo compatibility using animal models.
16. Wagner V, Dullaart A, Bock AK, Zweck A et al. (2006) The emerging nanomedicine landscape. *Nat. Biotech.* 24:1211–1217
17. Moghimi SM, Hunter AC, Murray JC et al. (2005) Nanomedicine: Current status and future prospects. *FASEB J.* 19:311–330.
18. Over the last 2 years, the National Institutes of Health has established a national network of eight Nanomedicine Development Centers, intended to serve as the intellectual and technological centerpiece of the NIH Nanomedicine Roadmap Initiative. These collaborative centers are staffed by multidisciplinary biomedical scientific teams including biologists, physicians, mathematicians, engineers, and computer scientists. Research conducted is currently directed toward gathering extensive information about the physical properties of intracellular structures to learn how biology's molecular machines are built. <http://nihroadmap.nih.gov/nanomedicine/fundedresearch.asp>

Chapter 6

The Need to Foster Revolutionary Science

As changes in this century's threat environment create strategic challenges – irregular warfare, weapons of mass destruction, disruptive technologies – this request places greater emphasis on basic research, which in recent years has not kept pace with other parts of the budget.

Secretary of Defense Posture Statement on the FY09 Budget, February 2008¹

Nanotechnology, as described in previous chapters, holds great promise and presents potential threats for US efforts in chemical and biological (CB) defense. In this rapidly changing world, the possibility of harm from nanotechnologies is real. A more likely possibility, however, is improved technologies across many defense and civilian sectors, and specifically in CB defense. It is increasingly apparent that in the next 30 years, CB defense could benefit substantially from a well-executed strategic vision for unique nanotechnology capabilities and nano-enabled science and technology.

In accordance with these emerging unconventional threats, the national security community must respond in unconventional ways. The technical challenges to realizing robust CB defense utilizing nanotechnology (described in Chapters 3 and 5) and the misuse of well-intentioned development (described in Chapter 4) are not the only barriers. Nontechnical barriers (including those noted in Chapter 1) must be overcome both to realize technical goals and to address the potential proliferation of nanotechnologically enabled CB weapons. This chapter will focus on institutional factors – domestic, international, and disciplinary – and policy recommendations.

Evolving Threats and Driving Forces

The changing nature of warfare, including threats to national security and the US response to those threats, is the main factor driving the need to foster revolutionary science. Throughout the Cold War in the twentieth century, the US homeland was perceived as secure from any major threat short of global war. The overarching threat of global nuclear war once dominated security issues. Today's threat regime is perceived very differently; the US is under threat from an expanded range of adversaries,

including present and emerging state powers, regional conflicts heightened by failing states that are US allies, and transnational extremist groups. Tactical threats are also more disperse, ranging from improvised nuclear devices to genetically engineered biological weapons and cyber attacks. This expansion has been fueled by the globalization of knowledge, information, and commerce that has proliferated critical technologies worldwide along with highly desired social and economic benefits.

In response to these changes, the US government has made significant modifications to both institutions and policies since 2001. Some of the most significant changes were the creation of Office of the Director of National Intelligence in 2006 and the formation of the Department of Homeland Security (DHS) in January 2003. The creation of DHS consolidated 22 offices and independent agencies from across the federal government and was the most comprehensive reorganization of the federal government in 50 years. It was also arguably the most significant transfer of private sector activity to government contracting since that time. Today, first responders across the nation are preparing for a range of situations once envisioned only in fiction. Concurrently, the DoD's role in homeland defense has expanded in both scope and complexity in the context of intra- and interagency priorities and missions.² The DoD's role includes the protection of US sovereignty, territory, domestic population, and critical defense infrastructure against external threats and aggression, or other threats as directed by the President.³

Concerns regarding emerging nonstate, nonaligned state, and traditional adversaries in the globalized world have prompted reassessment of defense against chemical, biological, nuclear (including improvised nuclear devices) or radiological attack during, conventional military, counterterrorism, counterinsurgency, and homeland defense operations. An increasing fraction of the military is executing special operations and support for stability, security, transition, and reconstruction operations has become a core DoD mission.^{4,5} To better defend the nation against emerging threats, nanotechnology – and its ability to improve countermeasure capabilities as well as to pose new threats – must be understood and developed with this overarching strategy in mind.

The Need for Strategic Vision

One path to address the threats and opportunities presented by emerging technologies is to develop a strategic vision to foster revolutionary science. To be effective, a strategic vision will encompass truly multidisciplinary approaches and incorporate comprehensive capability and threat analyses. It will endeavor to ensure the alignment of federal and nonfederal initiatives and present a unified federal effort to prevent proliferation.

Today, a significant fraction of the resources for CB defense and homeland security application is focused on near-term goals. Although exploiting “low-hanging fruit” and using nondevelopmental items and commercial off-the-shelf technologies may satisfy immediate goals, it is unlikely to adequately address an evolving threat or provide revolutionary capabilities. A more comprehensive strategy is to balance

more revolutionary approaches with the focus on near-term solutions and evolutionary improvements to currently deployed systems. The rapidly evolving nature of technology requires the US defense and homeland security communities to innovate to remain ahead of adversaries.⁶ Implementation of such a strategy begins with recognition of the need to leap ahead and embrace truly farsighted concepts while fostering integrated, multidisciplinary, and cross-cutting basic research approaches.

Fostering Breakthrough Discoveries

Strengthening science and fostering discovery and innovation has been a goal of the US government since the time Vannevar Bush published *Science the Endless Frontier* in 1945.⁷ In that seminal report, he argued that a nation dependent on others for its science will be slower and will be weakened as compared to science leading nations. He was also pessimistic about the ability of industry to execute basic research focused on scientific discovery owing to the practicality of their goals.

These questions remain today.⁸ A number of factors indicate that US scientific leadership in basic and applied research is at risk. These include the estimate that 70% of world research and development (R&D) is conducted outside the USA and that China is now the third largest investor in R&D behind only the USA and Japan.⁹ The USA has also reversed its status as a net exporter of high-technology products, from a \$54 billion surplus in 1990 to a deficit of more than \$50 billion in 2001.

The benefits of strong science extend to many national security priorities and needs. In addition to the generation of new discoveries, new knowledge, and improved understanding, a strong scientific research base enables technological superiority and reduces technology surprise. Further, the same basic research funding is used to educate scientists and engineers, providing a source of human talent - scientific expertise and engineering rigor - to support DoD technical efforts. Applying these recommendations 60 years ago resulted in a striking increase in Nobel prizes in the US as well as enabling overall leadership in national defense, public health, and public welfare.

A parallel strategy is needed today to enable the realization of revolutionary countermeasures and the anticipation of potential proliferation scenarios. The federal government holds the responsibility to foster innovative basic and applied science and technology through programs and policies that have historically led to scientific breakthroughs. Major discoveries are predicated by numerous small advances, embodied in multiple findings and processes that lead to a new way of thinking about a problem. In those cognitive realizations, the stage is set for the discovery of radical ideas and major breakthroughs that provide solutions to previously unrealized or unsolved problems. This strategy leads to challenges at the leading edge - or "bleeding edge"¹⁰ - of technology. Pursuit of concept with high risk and high payoff can be characterized by several factors. Most prominent is a lack of consensus, a situation where a number of potential competing mechanisms exist and which of them will lead to successful implementation (if any) is highly uncertain.¹¹

Such concepts lack wide dissemination and will have limited recognition of the new technology or product even in the trade press. Finally, a technology at the bleeding edge might be implemented by a single or few organizations seeking an advantage, but most industry experts are skeptical or openly averse.¹²

Pushing technologies beyond the bleeding edge and into applications depends on sustained research support, both institutional and financial. In order to realize the potential for revolutionary countermeasures and to anticipate potential proliferation scenarios, it is critical the federal government take steps to foster truly innovative basic and applied science and technology. Many efforts in CB defense in recent years have been driven by near-term demands. The structure and goals of both industrial and government research in this area has gone through any number of changes over the last 50 years, resulting in varying levels of success in fostering innovation. The opportunities for basic research in nanotechnology to impact CB defense are described in the eight cross-cutting research directions in Chapter 5.

A critical and often overlooked component of the ability to foster such revolutionary advancements is program management.¹³ Innovation is not aided by traditional project management requirements and their onerous enforcement can be devastating for innovation, especially those structures that were developed for lean manufacturing processes.¹⁴ Table 6.1 lists some characteristics of organizations that affect their ability to break through research barriers.

Additional factors affecting breakthrough science include the level of work at interdisciplinary junctions and the ability for scientists “to internalize a high level of

Table 6.1 Some characteristics of organizations that affect their ability to break through research barriers

Qualities of an organization that facilitate innovation and breakthrough discovery	Qualities of an organization that hamper innovation and breakthrough discovery
Moderately high scientific diversity, combined with the capacity to recruit scientists who embrace and internalize scientific diversity	High differentiation, with sharp boundaries among subunits (departments, divisions, and colleges)
High communication, with social integration of scientists from different fields through frequent and intense interaction	Hyperdiversity, to the degree that there cannot be effective communication among actors in different fields of science
Leadership has the capacity to understand scientific research directions, provides rigorous criticism in a nurturing environment	Bureaucratic coordination, with high standardization of rules and procedures
Bureaucratic flexibility that allows individual and small group autonomy and loose coupling with the institutional environment	Hierarchical authority with centralized decision-making about research programs, number of personnel, work conditions, or budgetary matters
	Resistant to partnering outside the institution, and anything “not invented here”

cognitive complexity.”¹⁵ To this end, mechanisms that span interdisciplinary boundaries should be increased. Interactions among scientists across disciplines, program managers across agencies, and potential operators across services are vital to facilitate innovation in disparate organizations.¹⁶ When individuals from a variety of backgrounds that bring a range of needed skills can’t communicate, innovation can get “bogged down in the abstract language of specialization and expertise.”¹⁷ This lesson is well-learned from biotechnology and other successful ventures that have translated breakthrough discoveries of genetics to application.^{18–21} One proven example to span boundaries is to develop clusters of small research institutes or interdisciplinary programs with multiple interrelated projects within physical proximity.²²

A productive level of horizontal and vertical communication is not easy for programs that have hierarchical histories and frequent external programmatic demands. Components of the program management team must function across both stakeholders and scientific disciplines. As disciplines and applications broaden – when nanotechnology meets CB defense, and when cutting edge scientists meet first providers – communication and innovation are no easy tasks. Internal and external strategic communications are an area needing more attention.

Challenges in Coordination of CB Defense Research

Two equally important challenges of CB defense coordination are one, bridging science and technology disciplines to foster multidisciplinary research, and two, resolving institutional and programmatic issues. In many cases, these challenges are not independent variables.

Defense against chemical or biological weapons necessarily involves the physical sciences, the life sciences, the medical sciences, and several engineering communities. Narrow demarcations of research into traditional disciplines – literally “old school thinking” – have become increasingly less likely to yield transformational technologies. Nanotechnology has emerged as an intrinsically interdisciplinary domain with the potential to bridge many disciplines. Notable examples are found in the design of sensors that use active complexes that bind DNA to carbon nanotubes; this was a joint effort of electrical engineers and computer scientists in one case²³ and originated in a physics and astronomy department research group in another.²⁴

Today, substantial cross-cutting between the medical and physical, chemical, and biological defense research communities already exists. For example, genetics research has long been incorporated into detection schemes in industrial pharmaceutical and medical device development. In some applied research and advanced development, however, islands of specialization remain isolated, for example, animal testing to satisfy regulatory requirements.

The benefits of improved coordination among large cross-cutting programs in both reduced cost and increased output have become very clear. Narrow demarcations

of research into traditional divisions will decreasingly yield the strategies and results needed to transform CB defense for the future.

Inter- and Intra-Agency Coordination of Nanotechnology

Organizational structure is critical for breakthrough science, as well as in enabling technology transition to applications.²⁵ This is especially important in order to actualize the revolutionary and transformation potential of nanotechnology in CB weapon defense.

Within the DoD, organizations have implemented individual strategies rather than a coordinated approach for developing, harnessing, and deploying nanotechnology. The lack of internal coordination for nanotechnology research was highlighted by the Congressionally mandated 2007 Defense Nanotechnology Research and Development Program Report.²⁶ The DoD, in coordination with other federal agencies, industry, and academia must take an active role in creating, implementing, and contributing to a truly multidisciplinary, cross-agency effort.

On the interagency level, the National Nanotechnology Initiative (NNI) Implementation Plan in 2001 highlighted CB detection as one of the nine Grand Challenges facing the nation at the start of the twenty-first century.²⁷ The nine Grand Challenges were incorporated into the more general overarching goals of the 2004 NNI Strategic Plan,²⁸ and biological and chemical defense still figures prominently in the NNI strategic vision. Within the 2007 NNI Strategic Plan, a number of cross-cutting, critical research needs relevant to CB defense are described, including R&D to enable early detection of life-threatening diseases, bionanotechnology, nanotechnology-based water purification and testing, future information processing technology, and predictive toxicology. The inclusion of the Chemical and Biological Defense Program on the NNI interagency coordinating body in early 2006 should help to better align nanotechnology-related research priorities for defense and homeland capabilities, requirements, and needs with the larger federal community. In 2008, the Department of Defense, for the first time in the history of the NNI, is funded with more nanotechnology research than any other federal agency.²⁹

Although many of the federal programs funding nanotechnology are science-driven, defense programs funding nanotechnology are generally mission-driven. The broadened participation on the NSET of lead research agencies involved in CB defense research can help to better align nanotechnology-related research priorities for defense and homeland capabilities, requirements, and needs with the larger federal community. The CBDP, DARPA, and DHS S&T can support this trend by reaffirming their commitment to supporting the NNI efforts.

As noted in Appendix A, interactions across federal agencies in CB defense research range from informal to formal coordination. Interactions in nanotechnology for CB defense, however, are less common. This represents an area to target

both domestically for federal agencies, as well as internationally through such avenues as the NATO Research and Technology Organization.

Technology Planning

In addition to interagency coordination, strategic technology planning is needed. A traditional form of technology planning, called “technology push,” describes a system where innovative basic and applied research enables previously unrealized capabilities. Over the last 20 years, the Defense Department and much of the federal research investment related to national and international security have shifted toward capabilities-based planning.³⁰ Capabilities-based planning is built on using national strategies and operating concepts to define critical capability needs; this has been referred to as “capabilities pull,” in which the requirements for a desired capability – such as stand-off detection or personal protection – drive the investment in technology. A successful technology planning process results in enhanced capabilities by integrating the operational need “pull” and technology push, resulting in the concept and capability solution development.

Within the DoD, as a project moves from basic research through advanced development, capability requirements becomes a larger part of the funding decision process. Unquestionably, capabilities-based planning has provided the US with the ability to conquer threats existing at the end of the Cold War and in the decades following. The ability of capability-based planning – as it is currently practiced through the federal acquisition process – to respond to the changing threat environment and future operational needs has yet to be proven, however.³¹

A balanced and flexible approach can ultimately be complementary to the more formalized requirements process for capabilities-based planning. While desired general capabilities such as biological detection or physical protection can be identified and used to pull the development of the countermeasure scenarios, specific requirements such as *which agents* and *what distance* or *to what exclusion level* are not always necessary and may deter innovation particularly in fundamental research and development. When the goal is to achieve revolutionary capabilities, such guidance can deter innovation.

Realization of truly revolutionary capabilities will require commitment to basic research aimed at fundamental understanding as well as acceptance of more technical and programmatic risk in applied research and advanced development. This is especially true in an emerging field such as nanotechnology. Currently, the words nanoscience, nanotechnology, or nanoengineering are all absent from the primary national defense and homeland security policy documents, further hampering their inclusion in capabilities-based planning.

Proactive program management will also be required to foster such innovative research. Historical precedent, while not predictive, has shown that revolutionary breakthroughs occur at interdisciplinary junctions,³² and federal support for research in the US is strongly biased toward disciplinary research.³³ In addition,

a flexible acquisition strategy that can balance push and pull is needed, such as “spiral development,” in which a minimum capability is fielded quickly and technological upgrades are incorporated throughout its lifecycle.

International Coordination

The highly transnational nature of nanotechnology R&D is a major consideration in reducing the risk of state-based misuse of nanotechnology for biological or chemical weapons. Any efforts to limit the proliferation and potential misuse of nanoenabled agents by nonstate actors must be international. Improved monitoring, cooperation, and understanding of technical capabilities across the globe will all aid in this effort.

Robust international agreements can lower the risk of terrorist applications by eliminating legal routes for terrorists to obtain chemical agents, precursors, or weaponization materials, and by minimizing transfers from states to nonstate actors through theft, deception, or other means. Efforts to strengthen the international regime to control transfers of dual-use chemicals are also important.³⁴ International efforts can be compromised by member countries of the Chemical Weapons Convention (CWC) that have not enacted domestic export-control legislation and nonmember countries with weak export controls. Additionally, the schedules of toxic chemicals and precursors covered by the CWC have not been updated since the treaty entered into force in 1997.^{35,36}

Effective incorporation of additional chemicals and precursors into this schedule will be needed to better respond to emerging and other novel agents, including those at the intersection of chemistry and biology^{37,38} and the potential intersection of both with nanotechnology. Many of the same issues, concerns, and criticisms are likely to arise for nanotechnology that arose in conjunction with the proposed additional protocols to the Biological and Toxin Weapons Convention (BWC) in the verification of suspected offensive weapons programs.³⁹ The ability to distinguish defensive nanotechnology efforts from offensive programs is expected to pose a difficult challenge.

Flexible approaches to nonproliferation and counterproliferation are important policy elements to reduce the risk of malevolent application of nanotechnology. Past practices and policies that do not take the international nature and prominent commercial nanotechnology sector into account are increasingly rendered inadequate.

Looking Forward

Bridges must be built between the world of science and the world of human relations, bridges which can give shape and purpose to our technology and breathe heart and soul into our knowledge.

Senator Sam Nunn⁴⁰

As the world looks to the future – whether dominated by extremist groups co-opting advanced weapons in the world of *Radical Game Changers* or *Annoying States* engaged in persistent regional conflicts in areas of strategic interest exploiting traditional agents – new adversaries and new science and technology will emerge. Choices made today that affect emerging revolutionary science and technologies, such as nanotechnology, will impact how ably the US and allies will respond. In the multidisciplinary world of the next century, the next frontier is finding ways to bridge the physical, life, and social sciences. Protecting from and deterring malicious actors will mean bridging communication gaps between scientists and operators, and building dialogue among the intelligence, policy, and economics fields. This effort, with a focus on nanotechnology for CB defense, illustrates the power and value of a truly multidisciplinary approach for strategic planning and could serve as a model for other science and technology programs.

The changing strategic environment in which the national security operation are planned and conducted impacts science and technology policy choices made today and affects how science and technology may play a beneficial or deleterious role in the future. The emerging field of nanotechnology has received global attention, and the world hangs on the cusp of new discoveries which may significantly alter military capabilities globally and may generate new threats against military and civilian sectors.

Some claims for the potential impacts of nanotechnology can seem fantastic; at times, differentiating rhetoric from reality can be nearly impossible. Of critical importance in considering the national and international security implications of nanotechnology – as well as such other emerging sciences as biotechnology and cognitive sciences – is that anticipated scenarios should be plausible within constraints of physical viability as well as likely within institutional capabilities. Action is needed to anticipate the threat of nanotechnology used for offensive CB weapons applications. The current technical limitations of nanotechnology are such that the present threat is low. The time to develop and establish strategic approaches and policy to limit or neutralize potential state or terrorist uses is now, rather than when such research applications appear inevitable. A better alignment of research priorities and planning guidance for nanotechnology will be needed to innovate and protect against newly emerging and growing threats.

At the core of the modern dual-use conundrum in technology is the recognition that almost all the equipment and materials needed to develop dangerous biological and chemical agents have legitimate uses in a wide range of scientific research and industrial activity.⁴¹ Technology from any source can enable disruptive capabilities and new capabilities can spur innovation. More awareness of disruptive technologies for commercial applications can anticipate uses of new technologies as weapons or countermeasures. The security community has a long and valuable tradition of fostering research to understand technology more fully; extending this to nanotechnology is needed to both employ and defend against new capabilities and emerging threats.

One of the most important ways that the government can improve their efforts is to create and foster communication channels between technically trained individuals,

especially those with experience in cutting edge research and those instrumental in policy development and implementation. Because nanotechnology is so heavily oriented to R&D, any constructive policy must engage both the public and private sectors, both nationally and internationally. Of particular interest are the small, high-technology start-up companies that arise near major research universities. To be effective, academic and industrial scientists must be willing to participate in meaningful dialogue and implement policies and protocols from within their ranks.

With the benefit of hindsight, it is clear that the USA and its allies would have greatly benefited from this type of strategic visioning in the early stages of biotechnology. Although some of the promises and potential security perils were addressed by the scientific community,⁴² the advantages of including the military and intelligence communities, along with the social science communities, in these discussions 30 years ago would have clear benefits today.⁴³ Similarly, a concerted, proactive effort leveraging multidisciplinary expertise is warranted sooner rather than later to address difficult security questions about prospects for nanotechnology. This includes the intersection with biotechnology, the cognitive sciences, and robotics in order to ensure that the US and its allies will have desired capabilities in 20 years from now.

One goal of the ambitious effort underlying this text was to better enable an informed debate on the potential role and impact of nanotechnology and emerging science on national and international security. Toward that end, several research directions in basic and applied science were identified that may foster transformational breakthroughs in nanotechnology-based CB countermeasures. This is complemented by a technically robust survey of the potential for proliferation and malfeasant cooption of emerging nanotechnologies. These findings were prioritized on a time-delineated roadmap that provides a basis for research direction decisions for CB nanotechnology countermeasures.

Dominance in both conventional and sophisticated military operations has been enabled in the US by a technological advantage in precision, speed, stealth, and tactical ISR as compared to adversaries. Equally innovative and more revolutionary capabilities will be required in order to ensure dominance and security in the twenty-first century, when adversaries span from *Dark Empires* of peer competitor nation-states to *A Thousand Points of Grayness* of disperse insurgencies.

Notes and References

1. Department of Defense (2008) Fiscal Year 2009 Department of Defense Budget Released. <http://www.defenselink.mil/releases/release.aspx?releaseid=11663>
2. Office of the Undersecretary of Defense for Homeland Defense (2006).
3. National Strategy for Homeland Security (2002) This differs from homeland security, defined as a concerted national effort to prevent terrorist attacks within the US, to reduce vulnerability to terrorism, and to minimize the damage and recover from attacks that do occur. DHS is the lead federal agency for incident management in the United States.

4. Department of Defense. (2005) Department of Defense Directive 3000.05. Military Support for Stability, Security, Transition, and Reconstruction (SSTR) Operations. <http://www.dtic.mil/whs/directives/corresp/pdf/300005p.pdf>
5. Department of Defense (2008) U.S. Army Field Manual on Operations, FM 3-0. http://www.dtic.mil/doctrine/jel/service_pubs/fm3_0a.pdf
6. Department of Defense (2008) Challenges to Military Operations in Support of U.S. Interests Defense Science Board Summer Study. http://www.acq.osd.mil/dsb/reports/2008-12-2007_SS_Vol_I.pdf
7. Bush V (1945) Science: The Endless Frontier. National Science Foundation. <http://www.nsf.gov/od/lpa/nsf50/vbush1945.htm>
8. National Academy of Science (2004) In 2004, the US Congress questioned whether the Department of Defense “investment in basic research has remained stagnant and is too focused on near-term demands.” Assessment of Department of Defense Basic Research. http://www.nap.edu/catalog.php?record_id=11177
9. Estimates adjusted for purchasing power.
10. The term “bleeding edge” originated in computer science to refer to software whose implementation risked reductions in stability and productivity; the bleeding edge is in front of the “cutting edge.”
11. These may include concepts that challenge Kuhn’s paradigms of normal science, described in ↑Kuhn TS (1996) *The Structure of Scientific Revolutions*, Third edition, University of Chicago Press.
12. Nilsen KD and Nilsen AP (1995) Literary metaphors and other linguistic innovations in computer language. *English Journal* 84:65–71.
13. Hollingsworth RJ (2007) *Fostering Scientific Breakthroughs and Radical Innovations*. Presentation to the Nanotechnology for Chemical and Biological Defense 2030 Workshop, Santa Fe, NM.
14. Lilien GL, Morrison PD, Searls K, Sonnack M, von Hippel E et al. (2002) Performance assessment of the lead user idea-generation process for new product development. *Manag. Sci.* 48:1042–1059.
15. Hollingsworth RJ (2007) High cognitive complexity and the making of major scientific discoveries. In: Arnaud Sales and Marcel Fournier, eds. *Knowledge, Communication and Creativity*. London and Thousand Oaks, California: Sage Publications. <http://history.wisc.edu/hollingsworth>.
16. Zucker LG and Darby MR (1996) Star Scientists and Institutional Transformation: Patterns of Invention and Innovation in the Formation of the Biotechnology Industry. *Proc. Natl. Acad. Sci.* 93:12709–12716. <http://www.sciencemag.org/cgi/reprint/304/5674/1117.pdf>
17. Janet R-D (2007) Bright ideas: Innovative minds don’t think alike. *New York Times*. <http://www.nytimes.com/2007/12/30/business/30know.html>
18. Hollingsworth RJ and Hollingsworth EJ (2000) Major discoveries and biomedical research organizations: Perspectives on interdisciplinary, nurturing leadership, and integrated structure and cultures. *Pract. Interdiscip.* 215–244. University of Toronto Press. <http://www.umu.se/inforsk/universitetsligan/hollingsworth.html>
19. Lemelson-MIT Program (2004) *Historical Perspectives on Invention and Creativity*. Massachusetts Institute of Technology School of Engineering. <http://web.mit.edu/invent/n-pressreleases/downloads/history.pdf>
20. Erwin DH and Krakauer DC (2004) Insights into innovation. *Science* 304:1117–1119.
21. von Hippel E (1988) *The Sources of Innovation*, New York: Oxford University Press. <http://stuff.mit.edu/people/evhippel/books/sources/Front%20Matter.pdf>
22. Hollingsworth RJ (2007) *Fostering Scientific Breakthroughs and Radical Innovations*. Presentation to the Nanotechnology for Chemical and Biological Defense 2030 Workshop, Santa Fe, NM.
23. Dwyer C, Guthold M, Falvo M, Washburn S, Superfine R, Erie D et al. (2002) DNA functionalized single-walled carbon nanotubes, *Nanotechnology* 13:601–604.
24. Staii C, Chen M, Gelperin A, and Johnson AT (2005) DNA-decorated carbon nanotubes for chemical sensing. *Nano Lett.* 5:1774–1778.

25. National Research Council (2006) *Accelerating Technology Transition*. Washington, DC: National Academy Press.
26. Defense Nanotechnology Research and Development Program Annual Report to Congress (2007) <http://nano.gov/html/res/pdf/DefenseNano2007.pdf>. The report highlighted the potential for nanotechnology to improve chemical and biological defense. "Large relative fluctuations" in funding for the CBDP were incorrectly attributed to the presence of Congressional additions, however. This statement could have been corrected by consulting the CBDP prior to release. In a further example of the lack of coordination, a reference to one memorandum of understanding between the CBDP's S&T management office and another federal agency incorrectly suggested that the CBDP's nanoscience research efforts were operating "under" another federal entity.
27. National Nanotechnology Initiative: The Initiative and its Implementation Plan. NSTC/NSET Report (2000) <http://nano.gov/html/res/nni2.pdf>. In the late 1990s, the federal coordination of nanotechnology efforts reached a broad scale with the charter of the National Nanotechnology Initiative (NNI). The Nanoscale Science Engineering and Technology (NSET) Subcommittee of the National Science and Technology Council's Committee on Technology coordinates planning, budgeting, program implementation, and review to ensure a comprehensive initiative. The NSET Subcommittee is composed of representatives from more than 25 agencies participating in the NNI.
28. National Nanotechnology Initiative (2004) Strategic Plan. http://www.nano.gov/NNI_Strategic_Plan_2004.pdf
29. National Nanotechnology Initiative (2007) Strategic Plan. p. 4.
30. Department of Defense (2006) *National Military Strategy to Combat Weapons of Mass Destruction*. p. 14.
31. Department of Defense (2006) *Defense Science Board Study Summer Study on 21st Century Technology Vectors*.
32. Hollingsworth RJ (2006) High cognitive complexity and the making of major scientific discoveries. In: Arnuad Sales and Marcel Fournier, eds. *Knowledge, Communication and Creativity*. London and Thousand Oaks, CA: Sage Publications.
33. Metzger N and Zare RN (1999) Interdisciplinary research: From belief to reality. *Science* 283:642–643.
34. Tucker JB (2007) Strengthening the CWC regime for transfer of dual-use chemicals. *CBW Conven. Bull.* 75:1.
35. *Getting Verification Right: Proposals for Enhancing Implementation of the Chemical Weapons Convention*. VERTIC (2002) <http://www.vertic.org/assets/Getting%20verification%20right.pdf>
36. In a statement, Ambassador Eric M. Javits, US Delegation to the Second Review Conference of the Chemical Weapons Convention, 7 April 2008, emphasized the need for increased funding and more frequent meetings of the CWC's Science Advisory Board, which considers new technological advances relevant to the treaty.
37. Dando M (2002) Scientific and Technological Change and the Future of the CWC: the Problem of Non-Lethal Weapons Disarmament Forum. 4:33–44. <http://www.unidir.org/pdf/articles/pdf-art1824.pdf>
38. Wheelis M and Danado M (2002) On the Brink: Biodefence, Biotechnology and the Future of Weapons Control. *The CBW Conven. Bull.* 58:3–7. <http://www.fas.harvard.edu/~hsp/bulletin/cbwcb58.pdf>
39. *Compliance Through Science: US Pharmaceutical Industry Experts on a Strengthened Bioweapons Nonproliferation Regime* (2002). Stimson Center Report No. 48 <http://www.stimson.org/cbw/pdf/ComplianceScience.pdf>
40. Nunn S (2008) Commencement Ceremony at Georgia Institute of Technology. <http://www.iac.gatech.edu/news/story.php?id=1893>
41. Atlas RM and Dando M (2006) The dual-use dilemma for the life sciences: Perspectives, conundrums, and global solutions. *Biosecu. Bioterror.: Biodefense Strat. Pract. Sci.* 4(3): 276–286.

42. Berg P, Baltimore D, Brenner S, Roblin RO. III, and Singer MF (1975) Summary statement of the Asilomar Conference on recombinant DNA molecules. *Proc. Nat. Acad. Sci.* 72:1981–1984.
43. Biotechnology Research in the Age of Terrorism (2004) http://www.nap.edu/catalog.php?record_id=10827

Appendix A

Roles and Missions of Chemical and Biological Defense Organizations

DOD's Chemical and Biological Defense Program

The Department of Defense Chemical and Biological Defense Program (CBDP) provides research, development, and acquisition programs to support passive defense capabilities, counterproliferation, and consequence management.¹ In support of counterproliferation, the CBDP provides operational capabilities tailored to the unique characteristics of the various chemical and biological weapons, including emerging threats, to facilitate passive defense and force protection. These capabilities also provide US forces the ability to rapidly and effectively mitigate the effects of a chemical or biological attack against deployed forces. In support of consequence management, the CBDP provides capabilities to respond to the effects of chemical or biological threats used against our forces deployed abroad and in the homeland.

The vision of the CBDP is to ensure that US defense operations remain unconstrained by chemical and biological (CB) effects. The CBDP mission is to provide CB defense capabilities in support of national military strategies. To accomplish this mission, the CBDP works to advance national interests by working effectively with other federal agencies, state and local governments, Congress, and the private sector.

The CBDP supports the passive defense charge of the Combating WMD mission, as outlined in the *National Military Strategy for Combating WMD*. The CBDP provides for WMD counterproliferation and consequence management. The CBDP is aligned into the four operational elements of the Combating WMD mission: *sense* (reconnaissance, detection, and identification), *shape* (information systems), *shield* (individual and collective protection, and medical prophylaxes and pre-treatments), and *sustain* (decontamination, restoration, and post-exposure medical capabilities, i.e., therapeutics and diagnostics). The CBDP does not perform intelligence collection on weapons development; this is performed by the intelligence community (Fig. A.1).

Research, development, and acquisition (RDA) of CB defense programs within the DoD are overseen by a single office within the Office of the Secretary of Defense (OSD). The Assistant to the Secretary of Defense for Nuclear, Chemical and Biological Defense Programs (ATSD(NCB)) serves as this single office. The ATSD(NCB) has designated the Deputy Assistant to the Secretary of Defense for Chemical and Biological Defense and Chemical Demilitarization Programs, which

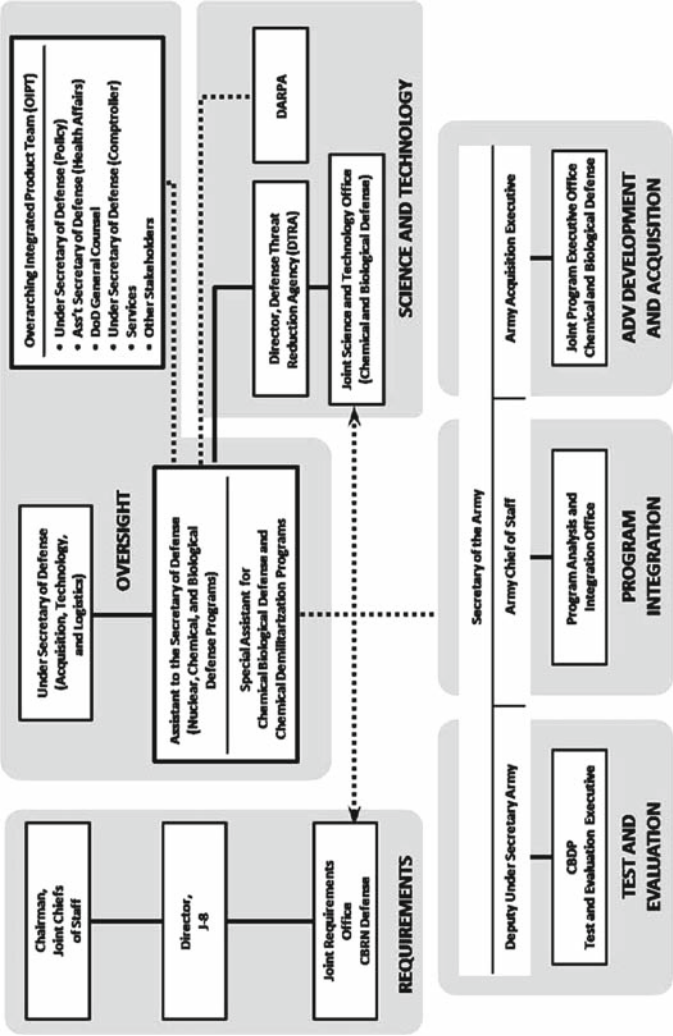


Fig. A.1 Chemical and Biological Defense Program organization

was called the Special Assistant for Chemical and Biological Defense and Chemical Demilitarization Programs (SA(CBD&CDP)) throughout 2007 and 2008, as the principal deputy for CBDP matters and the primary staff action office for ATSD(NCB) responsibilities.

All congressionally appropriated funds for DoD chemical and biological defense are overseen, managed, and executed through the CBDP, except specific exempted programs conducted by the Defense Advanced Research Projects Agency (DARPA) and Special Operations Command.

The Department of Defense's CBDP is guided by an implementation plan that translates National Strategy priorities into actionable guidance. The 2003 *Implementation Plan for the Management of Chemical and Biological Defense Program* outlines responsibilities for CB defense research and development within the DoD.

Specific strategic drivers and guidance for the CBDP research and development program include identification and exploitation of revolutionary, rather than evolutionary, technologies; investing in approaches that hold the potential for revolutionary capabilities to counter new threats; seeking out and taking advantage of advancements in information management, nanotechnology, bioengineering, multifunctional materials, and human performance studies; and exploiting nanotechnology and microsystems to achieve the capability to embed detectors into major defense acquisition program systems.

The CBDP is undertaking a number of efforts to actualize the revolutionary and transformational potential of nanotechnology in chemical and biological weapon defense. A major thrust, the Transformational Medical Technology Initiative (TMTI), is a revolutionary, interdisciplinary, and science-based strategy to counter the evolving and genetically engineered biological threats.² The TMTI program implements one of the key decisions in the 2006 Quadrennial Defense Review (QDR): develop broad-spectrum medical countermeasures against advanced bio-terror threats, including genetically engineered, intracellular bacterial pathogens, and hemorrhagic fevers. In the physical sciences (protection and hazard mitigation, detection, information systems), there is a nascent effort to exploit emerging technologies, to include the convergence of nanotechnology, biotechnology, information sciences, and cognitive sciences for revolutionary, integrated countermeasures.³

Major Organizations Managing the CBDP

Joint Requirements Office-Chemical, Biological, Radiological, and Nuclear Defense (JRO-CBRND). The JRO-CBRND is the office within DoD under the Chairman of the Joint Chiefs of Staff responsible for planning, coordination, and approval of joint Chemical Biological Radioactive and Nuclear (CBRN) defense operational requirements and serving as the focal point for Service, combatant command, and Joint Staff requirements generation. These responsibilities include development of CBRN defense operational requirements, joint operational concepts, and architectures for passive defense, consequence management, force protection, and homeland security.

Joint Science & Technology Office for Chemical and Biological Defense (JSTO-CBD). JSTO oversees the development and implementation of CB Science and Technology (S&T) programs authorized by ATSD(NCB) in alignment with Joint and Service capabilities requirements originating from the Joint Future operational Capabilities (JFOCs) and the Joint CBRN Defense Modernization Plan. Management responsibilities include the development and integration of the S&T program in response to OSD guidance. The JSTO-CBD works with the JPEO-CBD to ensure effective transition of S&T efforts to advanced development. Other JSTO-CBD responsibilities include the maintenance and leveraging of a robust Service S&T laboratory base to respond to DoD S&T needs, including test and evaluation, providing a DoD CB defense S&T liaison with various organizations (i.e., DARPA, Technical Support Working Group (TSWG), industry, academia, and other government agencies), providing support for DoD CB defense S&T international programs, and providing management and integration of CB Defense Advanced Concept Technology Demonstrations (ACTDs). The JSTO is colocated with the Defense Threat Reduction Agency's Chemical and Biological (DTRA-CB) Defense Directorate.

Joint Program Executive Office-Chemical Biological Defense (JPEO-CBD). The JPEO-CBD serves as the CBDP material developer and oversees life cycle acquisition management for assigned system acquisition programs. The JPEO-CBD provides centralized program management and Joint Service acquisition program integration for all assigned medical and nonmedical CB defense programs.

CBDP Test & Evaluation Executive. The Deputy Under Secretary of the Army for Operations Research (DUSA(OR)) serves as the CBDP T&E Executive and responsible for oversight of CBDP test and evaluation infrastructure, standards, processes, and procedures and ensures that CBDP systems are adequately tested and evaluated.

Joint Combat Developer for CBRN Defense (JCD-CBRND). Under the direction of the JRO-CBRND and supported by the Services and the US Coast Guard, the JCD-CBRND coordinates and oversees execution of Joint and multi-Service experiments used to validate the Joint Integrating Concept for CBRN Defense by systematically exploring new and innovative combinations of medical and non-medical doctrine, organization, training, materiel, leadership and education, personnel, and facilities capabilities. Experiments address the full spectrum of CBRN passive defense, force protection, consequence management, and homeland defense. The JCD-CBRND concept experiments complement the S&T and Advanced Development efforts managed by JSTO-CBD and the JPEO-CBD, respectively. The JCD-CBRND partners with the JFCOM in the broader DoD joint experimentation process. The US Army Chemical School (USAMCLS) provides myriad resources well suited for CBRND experimentation, and the JCD-CBRND takes maximum advantage of other personnel, equipment, and facilities available throughout each of the Services, and other government organizations to reduce costs, shorten timelines, and improve experimental designs. The JCD-CBRND strives to leverage planned exercises and other experiment venues outside of the CBDP.

Other Organizations

A number of federal agencies work in various levels of coordination with the CBDP. These organizations are both within and outside the DoD, and a number of them also coordinate with international entities. Although this is not a definitive list, it is included to show the extent and importance of CB S&T across the government.

Defense Advanced Research Projects Agency

The Department of DARPA supports high risk, high return research to support the warrior. The majority of DARPA's Chemical, Biological, and Radiological Defense efforts are sponsored by the Strategic Technology Office (STO) and the Defense Sciences Office (DSO).

Specific programs in STO include the development of new sensor and signal processing technologies and related devices to effectively provide these functional improvements for use in support systems to protect military personnel in both buildings and the battlefield. Additionally, STO is developing new technologies and design techniques for building construction and related infrastructure that will intrinsically protect personnel from exposure to these hazardous materials.⁴

DSO's major thrusts in CB defense are in therapeutics and biosensors. In therapeutics, DSO is exploring technologies that allow for the rapid production of millions of doses within a 16-week window. In biosensors, DSO is sponsoring research that is developing a new class of biosensors with tunable sensitivity and specificity that can be optimized for the threat level. An innovative approach for this is real-time modulation of protein conformation that implies the ability to sense engineered targets that avoid detection by highly specific agents, such as standard monoclonal antibodies.

DSO is also supporting technologies to detect biological agents at standoff distances via coherent nonlinear optical spectroscopy, laser pulse shaping techniques, and adaptive optics coupled to strategies that optimize the return signal from the agent under interrogation.⁵ A Memorandum of Understanding between DARPA and JSTO-CBD is in place to aid in the transition technologies for further development and into programs of record for potential acquisition by the services.

Department of Health and Human Services

The National Institutes of Health, under the auspices of The National Institute of Allergy and Infectious Diseases (NIAID), is taking the lead in conducting and supporting much of the research aimed at developing new and improved medical tools against potential bioterrorism agents. "Since 2001, NIAID has greatly accelerated its biodefense research program, launching several new initiatives to catalyze development of vaccines, therapies, and diagnostic tests."⁶

In addition, the National Science Advisory Board for Biosecurity (NSABB) acts as a federal advisory board within the National Institutes of Health. The Board consists of 25 voting members with a wide range of expertise, including molecular biology, microbiology, infectious diseases, laboratory biosafety and biosecurity, public health/epidemiology, health physics, pharmaceutical production, veterinary medicine, plant health, food production, bioethics, national security, biodefense, intelligence, law and law enforcement, scientific publishing, institutional biosafety committees, recombinant DNA, and export control.⁷ Some specific areas needing guidance include experiments that exemplify a notable or novel category of dual use research, and other instances where an institution seeks additional advice. The NSABB does not approve the conduct of specific experiments.

Department of Homeland Security

Two divisions research and analyze issues related to CB defense in the S&T Chemical and Biological Division in the Department of Homeland Security (DHS).

The Chemical and Biological Division “conducts analyses for better characterization and prioritization of the threat, develops detection systems to provide early warning of a possible attack so as to minimize exposure and speed treatment of victims, conducts forensic analyses to support attribution, and works with federal partners who have lead responsibilities in decontamination and restoration, agro-defense, and food security.”⁸ The biological countermeasures program develops a national biodefense architecture against high consequence biological threats and provides decision-makers and responders with the knowledge and tool to anticipate, present, prepare for, and respond to events. The program also works with the Department of Health and Human Services (HHS), the Department of Agriculture, the Environmental Protection Agency, and the Department of Justice, and coordinates the interaction between those agencies and the intelligence and defense communities. When appropriate, the directorate also incorporates bio-defense as part of an integrated chemical, biological, radiological, nuclear, and explosives defense across civil and military sectors.⁹

The Chemical Countermeasures Division within the DHS S&T program has the objective to develop a national chemical defense architecture. Goals within this purview are to enhance rapid recovery from chemical attacks and to develop pre-event assessment, discovery, and interdiction capabilities for chemical threats. Overall, the program seeks to minimize loss of life and economic impact from chemical attack and to enhance the capability to identify chemical attack sources.¹⁰

Appendix B

Attendees at the Workshop on Nanotechnology for Chemical and Biological Defense

Prof. Christer Aakeroy, Department of Chemistry, Kansas State University
Dr. George Bachand, Sandia National Laboratories
Dr. Jack Baggett, Chief Scientist, U.S. Army Medical Research Institute of
Chemical Defense
Dr. Arnold B. Baker, Chief Economist, Sandia National Laboratories
Dr. Patrick B. Black, U.S. Army ARDEC
Prof. Paul Bohn, Department of Chemical and Biomolecular Engineering,
Department of Chemistry, University of Notre Dame
Ms. Karen Bowen, OPNAV, U.S. Navy
Dr. Devon Byrd, General Dynamics, Advanced Information Systems (formerly
Chemical & Biological Technologies Directorate, Joint Science & Technology
Office (JSTO) for CB Defense, Defense Threat Reduction Agency (DTRA))
Prof. Rolf Bunger, Uniformed Services University of the Health Sciences (USUHS),
Defense Department
Dr. Jackquelyn Campbell, Defense Department
Dr. Patrick Carrick, Director, Physics and Electronics, Air Force Office of Scientific
Research
Mr. John P. Caves, Senior Research Fellow, Center for the Study of Weapons of
Mass Destruction, National Defense University
Prof. Esther H. Chang, Medical Center, Georgetown University
Mr. Frank Chapman, U.S. Army Maneuver Support Center
COL Matthew Coatsworth, Chief, Medical Modernization, HQ AFSOC/SGR, U.S.
Air Force
CAPT Kenneth Cole, Director M5B3, Future Plans & Strategies – Emerging
Science & Technology, Bureau of Medicine and Surgery, U.S. Navy
Prof. Vicki Colvin, Department of Chemistry, Department of Chemical Engineering,
Rice University
Dr. Joseph L. Corriveau, Director, Research & Technology Directorate, U.S. Army
Edgewood Chemical & Biological Center
Prof. Harold G. Craighead, School of Applied and Engineering Physics, Co-Director,
Nanobiotechnology Center, Cornell University

Mr. Fred Crowson, Division Chief, Chemical & Biological Technologies Directorate, Joint Science & Technology Office for CB Defense (JSTO), Defense Threat Reduction Agency (DTRA)

Dr. Jeff Depriest, Chemical and Biological Technologies Directorate, Joint Science & Technology Office for CB Defense (JSTO), Defense Threat Reduction Agency (DTRA)

LCDR Amanda Dion-Schultz, Bureau of Medicine and Surgery, U.S. Navy

Dr. Holly Dockery, Policy Development, Department of Homeland Security

MG John C. Doesburg, U.S. Army (ret), Principal Associate Director for Global Security Lawrence Livermore National Laboratory (LLNL)

Dr. Henry Dubin, Deputy Under Secretary of the Army, Testing and Evaluation Executive, Defense Department

Dr. Susan Durham

Prof. David Gorenstein, Associate Dean for Research, School of Medicine, Department of Biochemistry & Molecular Biology, University of Texas Medical Branch

Dr. Frank Gottron, Specialist in Science and Technology Policy, Congressional Research Service

Prof. David Guston, Director, Center for Nanotechnology in Society Department of Political Science, Arizona State University

COL Ben Hagar, Deputy Director, Chemical & Biological Technologies Directorate, Joint Science & Technology Office for CB Defense (JSTO), Defense Threat Reduction Agency (DTRA)

Prof. Naomi Halas, Department of Chemistry, Rice University

Dr. Wendy Hall, Director, Bioterrorism, WMD, and Science and Technology, Policy Directorate, Department of Homeland Security

Dr. Grant T. Hammond, Deputy Director, Center for Strategy and Technology, Air War College, U.S. Air Force

Dr. Diane E. Hannemann, Office of the Director, National Institutes of Health

Prof. H. James Harmon, Department of Physics, Oklahoma State University

Mr. Todd Harrell, Battelle, International Technology Assessments

Prof. Jim Heath, Department of Chemistry, California Institute of Technology

Prof. Craig L. Hill, Department of Chemistry, Emory University

Prof. Juan Hinestroza, Department of Textiles and Apparel, College of Human Ecology, Cornell University

Dr. Peter Hobart, Chief Scientist, U.S. Army Medical Research Institute for Infectious Diseases

Prof. Patricia Holden, Bren School of Environmental Science and Management, University of California at Santa Barbara

Prof. R. Rogers Hollingsworth, Department of History, University of Wisconsin at Madison

Dr. Cliff Hull, Senior Chemist/Advanced Sensors, Laboratory for Physical Sciences, University of Maryland at College Park

Prof. William Hunt, Department of Electrical and Computer Engineering, Georgia Institute of Technology

Prof. Joseph Hupp, Chair, Department of Chemistry, Northwestern University
Dr. Richard Jaffe, Senior Medical Advisor, ANSER, Inc, in support of the Office of the Special Assistant for Chemical and Biological Defense & Chemical Demilitarization (OSA(CBD&CDP)), Defense Department
Prof. A.T. Charlie Johnson, Department of Physics and Astronomy, Pennsylvania State University
Dr. Shaun Jones, Biodesign Institute, Arizona State University
Dr. Peter Jutro, Deputy Director for Science and Policy, National Homeland Security Research Center, Environmental Protection Agency
Dr. Michael Kaminski, Nuclear Forensics and Nanoscale Engineering, Argonne National Laboratory
Dr. Jonathan Kaye, National Homeland Security Research Center, Environmental Protection Agency
Prof. Kenneth J. Klabunde, Department of Chemistry, Kansas State University
Prof. Margaret E. Kosal, (through 31 July 2007) Science & Technology Advisor, Liaison to JSTO/DTRA-CB, Office of the Special Assistant for Chemical and Biological Defense & Chemical Demilitarization (OSA(CBD&CDP)), Office of the Secretary of Defense; (after 1 August 2007) Sam Nunn School of International Affairs, Georgia Institute of Technology
Dr. Thomas Lamkin, Air Force Research Laboratory, University of Cincinnati
Dr. Glenn E. Lawson, Senior Scientist, Dahlgren Division Naval Surface Warfare Center, U.S. Navy
Dr. Donald Leo, Virginia Polytechnic Institute and State University
Dr. Raymond A. Mackay, Director, Research & Technology, U.S. Army Edgewood Chemical & Biological Center
Dr. Jennifer S. Martinez, Los Alamos National Laboratory
Dr. Christophe L. McCray, Program Science Developer, Office of Naval Research
Prof. Martin Moskovits, Dean, Math, Life & Physical Science, College of Letters & Science, University of California at Santa Barbara
Dr. James Murday, Director of Physical Sciences, Office of Research Advancement, University of Southern California
Prof. Andre Nel, Chief, Division of NanoMedicine, Geffen School of Medicine, University of California at Los Angeles
Prof. Richard D. Noble, Department of Chemical & Biological Engineering, University of Colorado at Boulder
Dr. Aleksandr Noy, Theme Leader, Lawrence Livermore National Laboratories
CDR Thomas O'Donnell, Joint Requirements Office for Chemical, Biological, Radiological, and Nuclear Defense (JRO-CBRND), Joint Staff/J-8
Dr. Jeff Owens, Chemical & Biological Technologies Directorate, Joint Science & Technology Office for CB Defense (JSTO), Defense Threat Reduction Agency (DTRA)
Prof. Cengiz Ozkan, Department of Mechanical Engineering, University of California at Riverside
Prof. Mihri Ozkan, Department of Electrical Engineering, University of California at Riverside

Dr. Jerry Pate, Chemical & Biological Technologies Directorate, Joint Science & Technology Office for CB Defense (JSTO), Defense Threat Reduction Agency (DTRA)

CDR Mike Penny, Chief Medical Officer, Chemical, Biological, Incident Response Force (CBIRF), 4th Expeditionary Brigade, U.S. Marine Corps

Ms. Christine Peterson, Vice President, Foresight Nanotechnology Institute

Prof. Helen Purkitt, Department of Political Science, U.S. Naval Academy

Mr. Jean Reed, Special Assistant for Chemical and Biological Defense and Chemical Demilitarization Programs, Office of the Secretary of Defense

MG Stephen Reeves, Joint Program Executive Officer for Chemical and Biological Defense (JPEO-CBD), U.S. Army

Dr. R. Todd Reilly, Medical Science and Technology Division, Defense Department

Dr. Reynolds Salerno, Manager, International Biological Threat Reduction, Sandia National Laboratories

COL Patrick J. Sharon, Deputy Director, Joint Requirements Office for Chemical, Biological, Radiological, and Nuclear Defense (JRO-CBRND), Joint Staff/J-8

Mr. David J. Shaughnessy, Senior Analyst, U.S. Army Training and Doctrine Command

Dr. Sharon Shields, Senior Scientist, in support of the Chemical & Biological Technologies Directorate Joint Science & Technology Office for CB Defense (JSTO), Defense Threat Reduction Agency (DTRA)

Mr. Jared Silberman, Arms Control Counsel, U.S. Navy Strategic Systems Programs

Mr. John R. Steven, Deputy Director, Office of Security and Emergency Preparedness, Centers for Disease Control and Prevention

Prof. Michael S. Strano, Department of Chemical and Biomolecular Engineering, University of Illinois at Urbana-Champaign

Ms. Cindy Swim, Senior Team Leader, CB Detection, U.S. Army Edgewood Chemical and Biological Center

Dr. Chris Taitt, Research Biochemist, Naval Research Laboratory

Dr. Theodore Tarasow, Director, Biosecurity & Nanosciences, Laboratory, Lawrence Livermore National Laboratories

Prof. Gregory Timp, Department of Electrical and Computer Engineering, Beckman Institute, University of Illinois at Urbana-Champaign

Dr. Jeff Tsao, Sandia National Laboratories

LCDR Thomas D. Vandermolen, Maritime Science and Technology Center, U.S. Navy

Dr. Edward Wack, Director, Future Acquisition, Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD), U.S. Army

Prof. Zhong Lin (ZL) Wang, Department of Materials Science and Engineering, Director, Center for Nanostructure Characterization & Fabrication, Georgia Institute of Technology

Dr. Mike Weinrich, Director of the National Center for Rehabilitation Research in the National Institute of Child Health and Human Development, National Institutes of Health

Dr. Christian Whitchurch, Chemical and Biological Technologies Directorate, Joint Science & Technology Office for CB Defense (JSTO), Defense Threat Reduction Agency (DTRA)

Dr. Lloyd J. Whitman, Head, Surface Nanoscience and Sensor Technology Section, Naval Research Laboratory

Dr. Shara Williams, Bureau of Verification, Compliance, and Implementation, U.S. Department of State

Prof. Hai Xiao, Department of Electrical and Computer Engineering, University of Missouri at Rolla

Prof. Omar M. Yaghi, Department of Chemistry & Biochemistry, University of California at Los Angeles

LTC Richard Yaw, Operations Enterprise, Stockpile Surety Program, Defense Threat Reduction Agency

Appendix C

Agenda for the Workshop on Nanotechnology for Chemical and Biological Defense

Arrival Day Monday, January 29, 2007

Day 1 – Tuesday, January 30, 2007

7:00–8:00 a.m.:	Workshop Check-In
8:00–11:45 a.m.:	Plenary Opening Session
8:00–8:15 a.m.:	Workshop Welcome and Charge – Dr. Margaret E. Kosal, OSA (CBD&CDP) & DTRA-CB
8:15–8:45 a.m.:	Overview of the DoD Chemical and Biological Defense Program (CBDP) – Mr. Jean Reed, Special Assistant (CBD&CDP)
8:45–9:15 a.m.:	Bridging Science and Military Operations – MG John Doesburg, USA (ret) ORNL & University of Tennessee
9:15–9:45 a.m.:	Nanogenerators and Nano-Piezotronics for Self-Powered Nanodevices and Nanosystems – Prof. ZL Wang, Georgia Institute of Technology
9:45–10:00 a.m.:	Break
10:00–10:30 a.m.:	Military Operator’s View/Perspective of the Warfighter – CDR Mike Penny, CBIRF/4th Marine Expeditionary Brigade
10:30–11:00 a.m.:	Fostering Scientific Breakthroughs & Innovation – Prof. J. Rogers Hollingsworth, University of Wisconsin at Madison
11:00–11:30 a.m.:	Overview of the Scenario Process – Dr. Arnie Baker, Sandia National Laboratories
11:30–11:45 p.m.:	Workshop Roadmap – Dr. Margaret E. Kosal, OSA (CBD&CDP) & DTRA-CB
11:45–12:45 p.m.	Lunch (seating by focus group)
12:45–1:00 p.m.	Workshop Logistics Q&A
1:00–5:00 p.m.	Breakout Session 1a: Imagine/Prioritize 2030 Nanotechnology-Based Countermeasure Capabilities to Chem-Bio Threats
1:00 p.m.:	Focus group speaker gives overview of focus group area
1:40 p.m.:	Focus group leader reviews scenario process
1:50 p.m.:	Break
2:00 p.m.:	Imagine 2030 countermeasures

- 4:30 p.m.: Consistency review and viewgraph refinement for plenary report-out
- 1:00–5:00 p.m.: Breakout Session 1b: Imagine/Prioritize 2030 Nanotechnologically Enabled Proliferation Threats
- 1:00 p.m.: Focus group speaker gives overview of focus group area
- 1:40 p.m.: Focus group leader reviews scenario process
- 1:50 p.m.: Break
- 2:00 p.m.: Imagine 2030 nano-threats
- 4:30 p.m.: Consistency review and viewgraph refinement for plenary report-out
- Focus Group Speakers:
- Countermeasures*
- BW Detection and Diagnostics – Prof. A.T. Charlie Johnson, Pennsylvania State University
- CW Detection and Diagnostics – Prof. Michael Strano, University of Illinois at Urbana-Champaign
- Physical Protection – Prof. Omar Yaghi, University of California at Los Angeles
- Decontamination and Consequence Management – Prof. Craig Hill, Emory University
- Medical Countermeasures – Prof. Esther Chang, Georgetown University
- Potential Malfeasant Cooption of Nanotechnology*
- New or Nano-Enabled Biochemical Agents – Prof. Martin Moskovits, University of California at Santa Barbara
- Malfeasant Exploitation of Toxicological or Other Deleterious Health Effects – Prof. Vicki Colvin, Rice University
- Circumventing Vaccines and Evasion of Medical Countermeasures – Prof. David Gorenstein, University of Texas
- Self-assembled Materials and Devices to Molecular Assemblers – Prof. Cengiz Ozkan, University of California at Riverside
- 5:00–5:30 p.m.: Break
- 5:30–7:00 p.m.: Dinner (seating dispersed – participants to sit with members of other focus groups)
- 6:00–7:00 p.m.: Plenary Talk: Harnessing Systems Biology & Nanotechnologies for Meeting Chem-Bio Defense Challenges – Prof. Jim Heath, California Institute of Technology
- 7:00–7:05 p.m.: What just happened and what happens next – Dr. Margaret E. Kosal, OSA (CBD&CDP) & DTRA-CB
- 7:05–7:20 p.m.: Break
- 7:20–9:30 p.m.: Breakout Session 2a: Identify/Prioritize 2010 & 2020 S&T Capabilities and Infrastructure necessary to 2030 Nano-Enabled Countermeasure
- 7:20 p.m.: Identify/prioritize necessary 2020 S&T capabilities (cross-cut all quads)
- 8:10 p.m.: Break
- 8:20 p.m.: Identify/prioritize necessary 2010 S&T capabilities (cross-cut all quads)
- 9:10 p.m.: Consistency check

7:20–9:30 p.m.:	Breakout Session 2b: Identify/Prioritize 2010 & 2020 S&T Capabilities and Infrastructure related to 2030 Nano-Enabled Threats
7:20 p.m.:	Identify/prioritize necessary 2020 S&T capabilities (cross-cut all quads)
8:10 p.m.:	Break
8:20 p.m.:	Identify/prioritize necessary 2010 S&T capabilities (cross-cut all quads)
9:10 p.m.:	Consistency check

Day 2 – Wednesday, January 31, 2007

7:00–8:00 a.m.:	Continental Breakfast
8:00–10:30 a.m.:	Plenary Report-Out on Scenarios Focus group leader presents focus group findings and clarification questions Ballots will be distributed at beginning of session for prioritizations of 2030 scenarios and 2020 & 2010 S&T capabilities across focus groups and collected at dinner
8:00–9:15 a.m.:	Discussion: Countermeasures focus groups: 2030 Countermeasures and necessary 2010 & 2020 S&T capabilities
9:15–10:15 a.m.:	Discussion: Threats focus groups: 2030 Nano-threats and related 2010 & 2020 S&T capabilities
10:15–10:20 a.m.:	What just happened and what happens next
10:20–10:30 a.m.:	Break
10:30–12:00 a.m.:	Breakout Session 3a: Brainstorm “Blue-Team” Counter measures to Presented Nano-Enabled Threat Scenarios
Breakout Session 3b:	Brainstorm “Red-Team” Circumventions to Presented Nano-Enabled Countermeasures Scenarios
12:00–1:00 p.m.:	Breakout Session 4: Brainstorm research directions underlying or related to countermeasures or threats (Note: only research directions underlying countermeasures will be used as input to Breakout Session 5)
1:00–5:15 p.m.:	Free Afternoon
5:15–6:15 p.m.:	Dinner
5:45–6:20 p.m.:	Innovation in government and industrial research laboratories: What is possible? – Dr. Peter Hobart, USAMRIID
6:20–6:30 p.m.:	What just happened and what happens next – Dr. Margaret E. Kosal, OSA (CBD&CDP) & DTRA-CB
6:30–6:45 p.m.:	Break
6:45–9:00 p.m.:	Breakout Session 5: Delineate and Flesh-Out Overarching Research Directions
6:45 p.m.:	Identify/prioritize motivating countermeasures/motivating factors for research directions
7:20 p.m.:	Identify potential technical approaches to the research directions

8:20 p.m.:	Coffee break
8:25 p.m.:	Summarize the research direction
8:55 p.m.:	Identify two commentators per research direction to comment on its scientific and national security (policy) cases for Plenary Report-Out on Overarching Research Directions

Day 3 – Thursday, February 1, 2007

7:00–8:00 a.m.:	Continental Breakfast
8:00–10:30 a.m.:	Plenary Report-Out on Overarching Research Directions
Ballots for research direction prioritization (according to impact on science and national security) will be distributed at the beginning of this session and collected at conclusion of workshop	
10:30–10:35 a.m.:	What just happened and what happens next – Dr. Margaret E. Kosal, OSA (CBD&CDP) & DTRA-CB
10:35–10:50 a.m.:	Break
10:50–11:55 a.m.:	Breakout Session 6: Brainstorm Fostering Innovation within CBDP
12:10–12:30 p.m.:	Closing Remarks – Dr. Margaret E. Kosal, OSA (CBD&CDP) & DTRA-CB
12:30 p.m.:	Adjourn

Appendix D

Acronyms and Abbreviations

AAAS	American Association for the Advancement of Science
ACU	Army Combat Uniforms
ATSD(NCB)	Assistant to the Secretary of Defense for Nuclear, Chemical and Biological Defense Programs
BSE	Bovine spongiform encephalopathy
BWC	Biological and Toxin Weapons Convention
CB	Chemical and biological
CBDP	Chemical and Biological Defense Program
CBRN	Chemical, biological, radiological, or nuclear
CDP	Chemical Demilitarization Program
CNT	Carbon nanotubes
CWC	Chemical Weapons Convention
DARPA	Defense Advanced Research Projects Agency
DHS	Department of Homeland Security
DNA	Deoxyribonucleic acid
DOD	Department of Defense
DSB	Defense Science Board
DTRA	Defense Threat Reduction Agency
EF	Edema factor
FDA	Food and Drug Administration
GMR	Gigantic magnetic resistance
ICON	International Council on Nanotechnology
IMS	Indicator or ion mobility spectrometry
IO	Influence operations or information operations
IR	Infrared
JCD	Joint Combat Developer
JRO	Joint Requirements Office
JSLIST	Joint Service Lightweight Integrated Suit Technology
LF	Lethal factor
MEMS	Microelectronic mechanical systems
MOF	Metal organic frameworks
MOP	Metal organic polyhedra
MOPP	Mission-oriented protective posture

NCI	National Cancer Institute
NCL	National Characterization Laboratory
NEMS	Nanoelectromechanical systems
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NMR	Nuclear magnetic resonance
NNI	National Nanotechnology Initiative
NRL	Naval Research Laboratory
NSA	National Security Agency
NSET	Nanoscale Science Engineering and Technology
NTP	National Toxicology Program
OSA	Office of the Special Assistant
OSD	Office of the Secretary of Defense
PA	Protective antigen
PCR	Polymerase chain reaction
POM	Polyoxometalate
QDR	Quadrennial Defense Review
R&D	Research and development
S&T	Science and technology
SAW	Surface acoustic wave
SERS	Surface enhanced Raman scattering
SiNW	Silicon nanowires
siRNA	Small interference ribonucleic acid
SPR	Surface plasmon resonance
ssDNA	Single-stranded deoxyribonucleic acid
SSTR	Stability, security, transition, and reconstruction
SWNT	Single-walled carbon nanotubes
TAP	Trusted Access Program
TIC	Toxic industrial chemical
TMTI	Transformational Medical Technology Initiative
UAV	Unattended airborne vehicle
UV	Ultraviolet
WMD	Weapons of mass destruction

Single Use Acronyms

5GW	Fifth generation warfare
ACTDs	Advanced Concept Technology Demonstrations
BBB	Blood-brain barrier
cyt-c	Cytochrome c
DEAL	DNA-encoded antibody libraries
DOJ	Department of Justice
DUSA(OR)	Deputy Under Secretary of the Army for Operations Research

EPA	Environmental Protection Agency
ESOH	Environmental, Safety, and Occupational Health
FAIMS	Field-assisted IMS
FETs	Field effect transistors
HHS	Health and Human Services
IT	Information technology
JPEO	Joint Program Executive Office
JSTO	Joint Science & Technology Office
LETs	Light-emitting transistors
NIOSH	National Institute for Occupational Safety and Health
NRL	Naval Research Laboratory
NSABB	National Science Advisory Board for Biosecurity
NSF	National Science Foundation
NTAs	Nontraditional agents
RMA	Revolution in Military Affairs
SA(CBD&CDP)	Special Assistant for Chemical and Biological Defense and Chemical Demilitarization Programs
SBIR	Small Business Innovative Research
SOCOM	Special Operations Command
USDA	United States Department of Agriculture

Notes

1. Also known as the Joint Chemical and Biological Defense Program. Public Law 103–160, in section 1522 of title 50 United States Code.
2. 2007 Transformational Medical Technologies Initiative (TMTI) Report to Congress, <http://www.acq.osd.mil/cp/cbdreports/tmti.pdf>
3. “Opportunities at the Intersection of Nanoscience, Biology and Computation,” JSR-02-300, November 2002, <http://www.fas.org/irp/agency/dod/jason/nanoint.pdf>
4. <http://www.darpa.mil/sto/chembio/index.html>
5. <http://www.darpa.mil/dso/thrusts/bwd/index.htm>
6. <http://www3.niaid.nih.gov/biodefense/>
7. <http://www.biosecurityboard.gov>
8. http://www.dhs.gov/xabout/structure/editorial_0531.shtm
9. http://www.dhs.gov/xres/programs/editorial_0540.shtm
10. http://www.dhs.gov/xres/programs/editorial_0541.shtm

Index

A

Artificial immune system, 55–57

B

Biodefense, 13

Biological agent detection and diagnostics

field equipments, 51–52

pathogen nucleic acid sequencing, 51

Biological and toxin weapons convention (BWC), 8, 128

Bovine spongiform encephalopathy (BSE), 92

Bush, G.W., 12

Bush, V., 11, 123

C

Carbon nanotubes (CNTs)

molecules, translocation, 91–92

SWNTs, 92

Chemical agent detection and diagnostics

field-assisted IMS, 48–49

IMS, 48

mass spectrometry techniques, 49–50

NMR spectrometers, 49

SAW dual delay line device, 48

Chemical and biological (CB) defense

2004 DHS strategic plan, 14

DoD investment, 14

infrastructure, 115

nanomaterials, 107

National Strategy, 13

research

inter-and intra-agency coordination,
126–127

International coordination, 128

programs, 108

technology planning, 127–128

Chemical and Biological Defense Program (CBDP), 19

Chemical and biological weapons,
1, 4, 12, 13

Chemical weapons convention (CWC), 8, 128

Chiarelli, P.W., 2

Clinton, B., 12

CNTs. *See* Carbon nanotubes

Cold war, 1, 2, 4, 11

Countermeasures, chemical and biological
decontamination

advancement essential components,
74–75

demilitarization and wide-area, 70–71
pre and post-exposure protection,
64–70

detection and diagnostics

augmenting sensitivity levels, 43

methods, 43–52

nanoscale sensors, 43

scenarios, 44

medical

2010 and 2020 design challenges,
76–77

non-technical barriers, 80

science and technology capabilities,
75–76

technical challenges, 79–80

nanoscale progress, 29–30

physical protection

advanced implications, 32–33

JSLIST garments, 32

mission-specific threats, 31

MOPP levels, 31–32

pathways, 38–42

possible solutions, 33–38

warfighter protection, 30

research, 80

D

Decontamination
 advancement essential components, 74–75
 all-purpose, 68–69
 demilitarization and wide-area, 70–71
 indoor, 69–70
 malicious design, 67
 and post-exposure protection
 CB weapons, 64
 nanocrystalline material, 66
 nanomaterial properties, 64–65
 nanostructural possibilities, 67
 properties, 65
 and pre-exposure protection, 71–72
 scenarios, 63

Defense Science Board (DSB), 11

Department of Defense (DoD)

 global environment, 11

 investment, CB defense, 14

Department of Homeland Security

 (DHS), 122

Detection and diagnostics

 advancement essential components, 60–62

 CB countermeasures, pathways

 core capability requirements, 57–58

 fields and capabilities, 59–62

 technology opportunities, 58–59

 methods

 artificial immune system, 55–56

 biological agent, 51–52

 chemical agent, 48–51

 multielement sensor arrays, 44

 point detection, 45

 pre-symptomatic disease, 55

 remote detection, 45–48

 potential improvements, 2030

 embedded autonomous sensors, 52

 nansenabled technologies, 54–55

 silica nanotubes, 53–54

DHS. *See* Department of Homeland Security

DNA-encoded antibody libraries, 52

DoD. *See* Department of Defense

DSB. *See* Defense Science Board

Drexler, K.E., 5, 98

F

Feynman, R., 5

Forward operating sites (FOS), 31

G

Gingrich, N., 5

Globalization, 2, 4–5, 11

H

Hammes, T.X., 89

Hopps, J.H., 8

I

Improvised explosive devices (IEDs), 33

Information operations (IO), 95–96

Information technology

 advances, 4

 and biotechnology, 2

International Council on Nanotechnology

 (ICON), 108

Ion mobility spectrometry (IMS), 48

J

Jeremiah, D.E., 8

Joint service lightweight integrated suit

 technology (JSLIST), 31

K

Krulak, C.C., 1

M

Magnetic nanoparticle-based gene

 delivery, 93

Manufacturing readiness levels (MRL), 36

Mass spectrometry techniques, 49–50

Medical countermeasures

 advancement essential components, 74–75

 2010 design challenges, 76–77

 2020 design challenges, 77–78

 nanotechnological growth, 72

 NIH, 72–73

 science and technology capabilities, 75–76

 technical challenges, 78–80

Metal organic frameworks (MOF), 35, 68

Mission-oriented protective posture (MOPP)

 clothing solutions, 32

 levels, 31–32

N

NanoCBD2030, 19, 26–27

Nanoelectromechanical systems (NEMS),

 114, 115

Nanomachines, 97–98

Nanotechnology characterization laboratory

 (NCL), 108

National Institute for Occupational Safety and

 Health (NIOSH), 108

National Institutes of Health (NIH), 72, 118
 National Nanotechnology Initiative (NNI), 7,
 108, 126
 National Science Foundation (NSF), 12
 National Security Agency (NSA), 37
 National Toxicology Program (NTP), 108
 Nuclear magnetic resonance (NMR), 49, 55
 Nunn, S., 128

O

Omics

molecular profiling, 109
 related technologies, 108
 in systems biology, 110

Opportunities and challenges

environmental threat, response, 1–2
 factors
 executive agency directives, 13–15
 federal guidance, 12–13
 operator needs, 9–10
 science vs. national security, 10–12
 technological progress
 consequences, 8–9
 globalization, 4–5
 International investments, 7–8
 nanoscale, revolutionary, 5–6
 science to application, 6–7
 warfare, changing nature
 military strategy changes, 3–4
 non-state actors, 2–3
 terrorists, international and domestic, 3
 world domination, 2

P

Physical protection

implications, 32–33
 MOPP levels, 31–32
 nanoscale materials technology, 30
 pathways
 2010 and 2020 design challenges,
 39–42
 hydrolytic and oxidative mechanisms, 38
 materials production, 38
 personnel wear helmets, 32
 possible solutions
 IEDs, 33
 interacting active sensors, 34–35
 large-scale disruptive weapons, 34
 nanoenabled materials, 37
 nanoparticle agglomeration and
 clustering, 35
 operational considerations, 37–38

personal protective ensemble, 39
 structural components, 36

Point detection, 45

Potential malfeasant co-option

bio- and nanoenabled influence
 operations
 bio-IO threats, 96
 influence operations, 95–96
 biochemical weapons, novel agents
 aerosol delivery, 91
 CNTs, 91–92
 Creutzfeldt-Jakob disease, 92
 DNA and nonviral delivery, 92–93
 drug delivery, 90
 medical countermeasures
 anthrax toxin, 96
 immune system pathways, 97
 molecular self-assemblers
 scientific community, 97–98
 self-assembly, 98
 self-replication, 98–99
 nanoparticles, toxic/deleterious health
 effects
 inhalation/ingestion, 93–94
 potential toxicity, 94
 TiO₂ particles, 95
 proliferation threats, 89–90

Process implementation

“four worlds”, envisioning
 countermeasure development, 25
 technology pace, 24
 threats, 25–26
 goals, 21
 scenario
 characteristic descriptors, 22
 planning, 20, 22–23
 roadmap and prioritize, 26–27
 2030 worlds, creation
 annoying states, 23–24
 dark empires, 24
 radical game changers, 23

Putin, V., 7

Q

Quadrennial defense review (QDR), 11

R

Remote detection

electromagnetic wave scattering, 46
 nanowire sensor arrays, 46–47
 SERS, 48
 SNAP nanowires, 47

- Research priorities and directions
 - biological systems, bio-to-nano worlds
 - biocompatibility, 111–112
 - biomimetic systems and devices, 111
 - discovery-based, 103–104
 - goals, 104
 - interdisciplinary, 104–105
 - modeling and simulation
 - atomic level, 113
 - interoperability and coupling, 113–114
 - risks, 114
 - nanomaterials structure and function
 - nanoscale properties and reactivity, 105–107
 - physiologic properties and reactivity, 107–108
 - nature, 103
 - power and energy, 114–115
 - self-assembly, 112
 - systems biology
 - multivariate nature, 108
 - revolutionary countermeasures, 109
 - technical hurdles, 109–110
 - top-down and bottom-up approach, 110
 - systems integration and engineering
 - application, 115
 - database, 116–117
 - materials, 116
 - translational medicine
 - infrastructure, 117–118
 - nanoenabled products, 117
 - Revolutionary science
 - breakthrough discoveries
 - bleeding edge, technology, 123–124
 - genetics, 125
 - organizations, research barriers, 124
 - science leading nations, 123
 - CB defense research
 - inter-and intra-agency coordination, 126–127
 - International coordination, 128
 - technology planning, 127–128
 - strategic vision, 122–123
 - threats and driving forces, 121–122
- S**
- Schwartz, P., 20, 22
 - Silicon nanowires (SiNWs), 49, 52
 - Single-walled carbon nanotubes (SWNTs), 92
 - Stability, security, transition, and reconstruction (SSTR), 3, 122
 - Superlattice nanowire pattern transfer (SNAP), 46–47
 - Surface acoustic wave (SAW), 48
 - Surface enhanced Raman scattering (SERS), 48
 - Surface plasmon resonance (SPR), 49–50
- T**
- Technology push, 127
 - Technology readiness level (TRL), 36
 - TGN1412 antibody, 97
 - Toxic industrial chemicals (TICs), 31, 33, 37, 54
 - Toxic industrial materials (TIMs), 37